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DEPARTMENT OF  
HEALTH, EDUCATION  
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Health Service

National Institutes of Health

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# **A History of Cancer Control in the United States 1946-1971**

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**Book One**

**A History of  
Scientific and  
Technical  
Advances in  
Cancer Control**

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# A History of Cancer Control in the United States 1946-1971

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## Book One

V. 2

## A History of Scientific and Technical Advances in Cancer Control

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Prepared by the  
History of Cancer Control Project,  
UCLA School of Public Health  
pursuant to Contract No. NOI-CN-55172,  
Division of Cancer Control and  
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DEPARTMENT OF  
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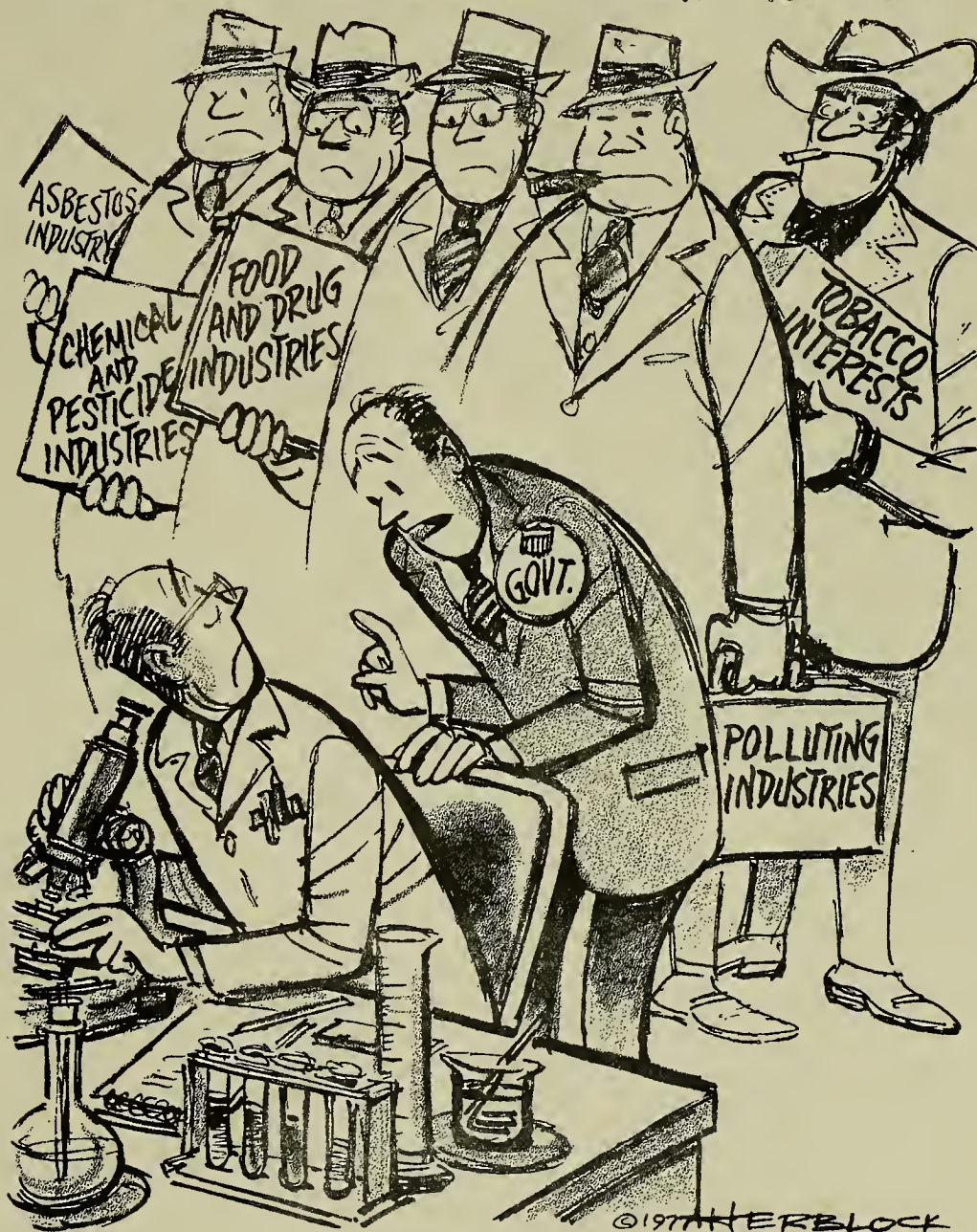


BOOK ONE

A HISTORY OF SCIENTIFIC AND TECHNICAL ADVANCES  
IN CANCER CONTROL



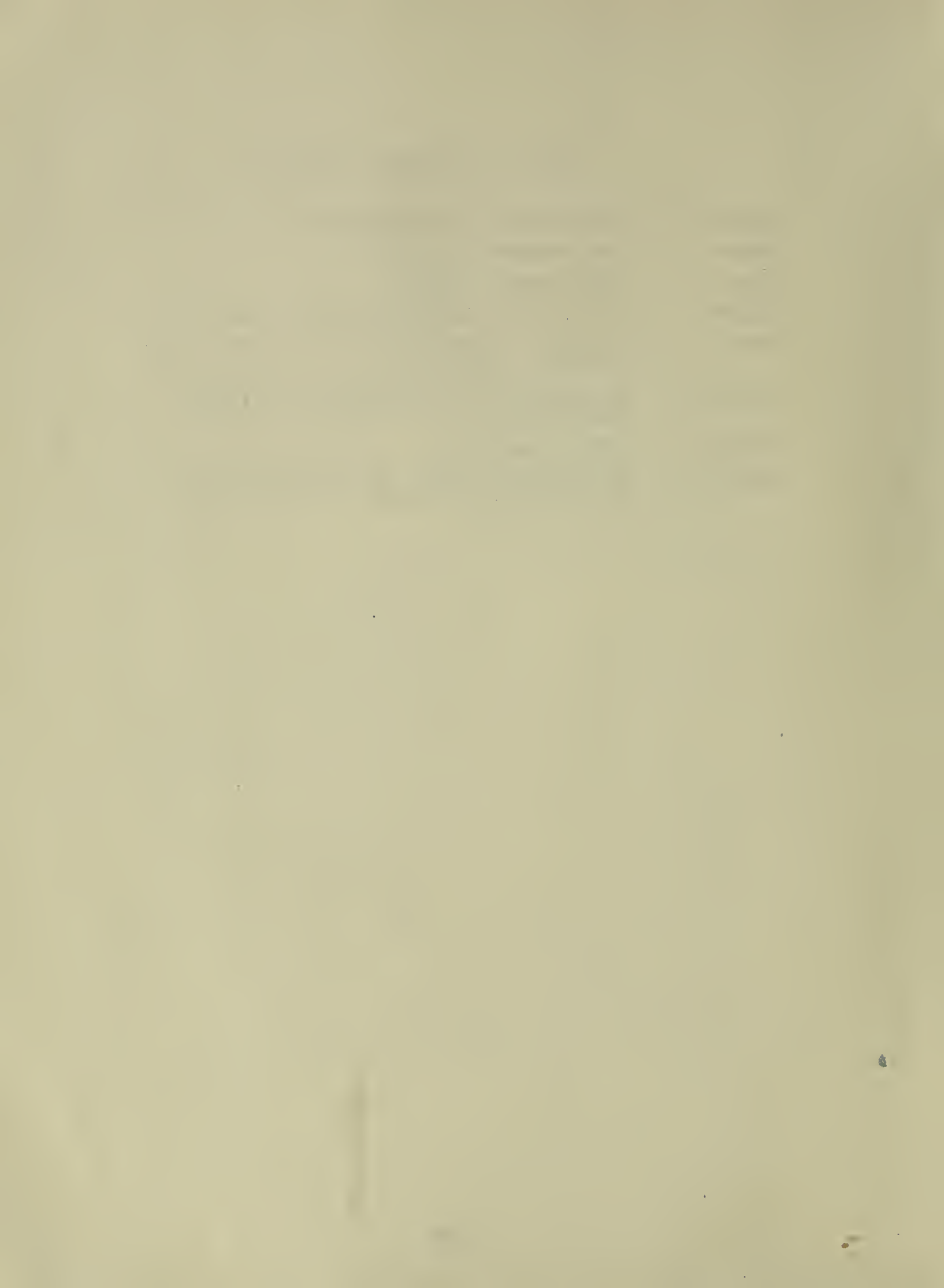
"COULD YOU HURRY AND FIND A CURE FOR CANCER?  
THAT WOULD BE SO MUCH EASIER THAN PREVENTION"





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## CHAPTER 1

### OCCUPATIONAL CARCINOGENESIS

#### Introduction

Occupational carcinogenesis has a two century history dating back to the observations of Dr. Percival Pott, a London surgeon, who in 1775 first noted the high rate of scrotal cancer among young boys who toiled as chimney sweeps. (1) Pott's findings, which were really coincidental with the onset of the Industrial Revolution, were to be followed by others. In 1822, Dr. A. Paris, another English physician, noted the high incidence of skin cancer among workers exposed to inorganic arsenic. (2) By the early 1900s, the cancer-causing hazards of certain dyestuffs, cutting oils, and radioactive substances were also becoming evident. (3) For the most part, the pre-twentieth century discoveries in occupational carcinogenesis took place in Western Europe where industrialization generally had proceeded further than in the United States.

Throughout this early period, interest and progress in occupational cancer control was slight; and in the United States it was virtually nil. The lone exception to this pattern was the relatively rapid progress recorded in the first third of the

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Principal Researcher/Writer: Larry Agran



twentieth century in dealing with radiation hazards from X-rays. This progress was no doubt owing in large measure to the fact that medical practitioners and technicians were themselves among those at highest cancer risk from X-irradiation.

In 1915 an American, Frederick L. Hoffman, statistician for the Prudential Life Insurance Company and Chairman of the Committee on Statistics for the American Society for the Control of Cancer, added considerably to the knowledge of occupational carcinogenesis with his publication of an impressive volume entitled The Mortality from Cancer Throughout the World. Hoffman's thesis was that cancer was becoming "a real menace to all civilized mankind...an increasing menace to civilized peoples." (4) In support of this thesis, Hoffman offered a vast array of tables, charts, and graphs--many of these highly suggestive of the industrial and occupational origins of certain cancers.

Despite the fervor with which Hoffman pled the case for occupational cancer control, the record of American industry throughout the 1920s and 1930s reveals little evidence of responsiveness to the hazards at hand. Hoffman's efforts would have to be carried further by others, most notably Dr. Wilhelm C. Hueper.

#### Wilhelm C. Hueper

During the years 1938 - 1941, Dr. Wilhelm C. Hueper, at that time a little known research pathologist, studied daily in the Philadelphia Library of Medicine. In the course of those four years, he spent thousands of hours surveying every available



article which even remotely implicated specific chemical or physical agents in the causation of human cancer. Finding that the medical librarian took a genuine interest in his research, Hueper would regularly submit long lists of journal articles which he wanted to read; each time he did this, the librarian saw to it that the journals were pulled from the shelves and neatly stacked, ready for his review the following day. In pursuing his research Hueper drew heavily upon Hoffman's work. Similarly, he referred frequently to the contributions of C. D. Haagensen, (5) and E. L. Kennaway, (6) the eminent British epidemiologist.

After his four-year research effort--the German-born Hueper later described it as looking for "one piece of dirt leading to another" (7)--he had amassed the evidence necessary to write a monumental 896-page tome entitled Occupational Tumors and Allied Diseases. (8) Published in 1942, the book, like Hoffman's earlier work, documented the existence of a series of high-risk occupations for cancer. But Hueper went further; he identified the suspected or recognized cancer-causing agents (carcinogens) associated with certain occupational cancer epidemics, and he argued for a cancer prevention strategy consisting of effective control measures to match the hazards of what he termed "the new artificial environment."

While the inanimate, exogenous environment, to which man and animals are exposed, depended through the preceding ages mainly upon the locally prevailing geological and climatic conditions determining the type of fauna and flora and represented in this sense a part of the natural environment, the gigantic growth of modern industry occurring in its main portion within the lifetime of men now living,

i.e., within the last one hundred years, has introduced numerous artificial, heretofore unknown, exogenous factors in constantly increasing number and variety. The creators and beneficiaries of the industrial development are thereby made potential victims of health hazards which cause numerous and diverse acute as well as chronic and insidious diseases never observed before. (9)

Just as scientists learned in the nineteenth century that numerous pathogenic micro- and macro-organisms were the environmental agents of serious disease, so too, Hueper argued, the steady increase in the incidence of cancer since 1900 was due to the interaction of the human cells with a burgeoning variety of specific chemical and physical agents, some of them highly carcinogenic.

More than a statement on occupational cancer, Hueper's Occupational Tumors stands today as a singular contribution to the modern theory of environmental carcinogenesis. But, when it was published in 1942, the book failed to attract attention commensurate with its significance. The timing of its publication could hardly have been worse, coming as it did only weeks after the Japanese attack on Pearl Harbor. In Hueper's words, "It was a difficult time to try to interest people in the loss of life." (10)

Among the multiple carcinogens which Hueper identified in Occupational Tumors were benzidine, beta-Naphthylamine, and several other aromatic amines used in a wide variety of industrial processes and associated with a major increase in bladder cancer, most notably among exposed dyestuffs workers. In 1974, 32 years after the publication of Hueper's text, the newly established federal Occupational

Safety and Health Administration (OSHA) was prompted to adopt national standards intended to limit worker exposure to 14 carcinogens. (11) Among the 14 were benzidine, beta-Naphthylamine, and other aromatic amines--the very same substances which Hueper had documented more than three decades before as potent occupational carcinogens. What were the institutional forces responsible for this tragic hiatus? Hueper's career provides some instructive insights into the barriers to effective preventive policies.

In November of 1934, Dr. Hueper went to work for E. I. DuPont in New Jersey. He was employed because of his familiarity with the problem of bladder cancer among European dye workers. According to Hueper, he was hired with the understanding that he was to work upon "the puzzle of bladder cancer in dye workers." (12) At that time, DuPont officials were of the view that the problem was essentially limited to their European dye workers since there were few known cases in their American dye works. Hueper believed otherwise. His knowledge of the European experience, first documented by Dr. Ludwig Rehn in Germany in the late 1800s, (13) led him to the conclusion that there was a latent period of approximately 15 years between effective exposure to dyestuffs and the onset of bladder tumors. And, since DuPont's American dye operations were relatively new, established during World War I, Hueper contended that it was just a matter of time until the malignancies appeared among American workers. Then, only a few months later, DuPont researchers conceded that, indeed, some of their American workers were being diagnosed for bladder cancer. The researchers reported to Hueper

that they had confirmed a total of 23 cases. He responded, "You will get more. This is a going concern now." (14)

With this background, Hueper spent the next several years working on the bladder cancer problem at DuPont. His work included experiments with dogs, injecting them with beta-Naphthylamine; finally, in 1938, he concluded that beta-Naphthylamine was at least one of a number of aromatic amines responsible for the outbreak of bladder tumors among DuPont workers. (15) Hueper's separation from DuPont followed shortly after this breakthrough. He describes the circumstances of his termination.

I insisted that [my] observations should be published. My philosophy of controlling cancer hazards in industry was fundamentally different from that of the DuPont Company. The management at that time took the view that such observations were strictly the business of the management and didn't even need to be directly communicated in all their tragic implications to the workers. My viewpoint was that as soon as the management became aware that a possible cancer hazard might exist in any of their operations, the workers should be informed why control measures were being taken so that they got the full cooperation of the men. (16)

In 1976, nearly 40 years after Hueper was dismissed from DuPont, there was grim vindication of his forthright views on the moral responsibility of corporate management. By its own admission in February, 1976, the DuPont company revealed that its records showed 339 of 2,000 workers exposed to beta-Naphthylamine during the years 1919 to 1955 fell victim to bladder cancer. (17)

After the publication of his book in 1942, Hueper continued his



investigations with the Warner Institute for Therapeutic Research until, in 1948, recognition of his contributions led to his appointment as Chief of the National Cancer Institute's Environmental Cancer Section in the Cancer Control Branch. Almost before he had moved into his office, he became embroiled in controversy. Amid the then boundless enthusiasm surrounding atomic power, Hueper harbored grave concerns about the evidence pointing to severe lung cancer hazards to uranium workers. In light of this concern, one of his first steps was to overcome objections of the Atomic Energy Commission and win approval of an investigation of cancer rates among uranium ore miners in the Rocky Mountains. With the study well underway, the doctor was invited to present a paper to a meeting of the Colorado State Medical Society. The subject: environmental and occupational cancer hazards on the Colorado Plateau. In his draft paper, Hueper referred to the European studies dating back to 1879 which indicated staggering lung cancer rates among radioactive ore miners. (18) Before the paper could be delivered, Hueper was ordered to delete mention of these studies on the grounds that dissemination of such information among members of the Colorado medical profession was not in the public interest. (19) Finding this command irreconcilable with his conscience as a scientist, he withdrew from the speaking engagement rather than deliver a censored manuscript.

Another far more serious incident occurred in 1952. It apparently grew out of Hueper's work with Dr. Thomas Mancuso, demonstrating rampant lung cancer--up to 16 times the expected rate--among American chromate workers. (20) Hueper found the lung cancer incidence among

white workers employed in one large chromate-producing plant to be 40 times normal; among non-white workers the lung cancer rate was 80 times normal. (21) The emerging evidence suggested that the entire chromate industry was implicated in what appeared to be a major outbreak of occupational cancer. Dyes, uranium, chromates--it seemed to Hueper that the dimensions of the entire occupational cancer problem were mushrooming before his eyes. Naturally, the meaning of all this was not lost on those with threatened economic interests. Dr. Hueper recalls what happened.

My active direction of epidemiologic studies on occupational cancer hazards and cancers in American industries was forcefully and abruptly brought to a halt in 1952 by an order of the Surgeon General. [This followed] a protest to the Public Health Service by Dr. A. Lanza, medical advisor to the chromate-producing industry, on behalf of his clients. In this protest, promoted by the industry as an action of "self-defense," it was alleged that my activities were detrimental to their interests. As the result of this intervention by a medical consultant of private industry, I was forbidden to contact thereafter state health departments and industrial concerns on all matters of occupational cancer. [I was ordered] to discontinue all field work on this subject and to restrict my activities entirely to experimental research... in the laboratory. (22)

This order, relegating Hueper to work removed from the front lines of any assault on occupational cancer, was never rescinded. In a 1959 speech, prepared for delivery to the Executive Council of the AFL-CIO, Dr. Hueper, still the titular Chief of the Environmental Cancer Section, asserted the deleterious effect of these events on the effort to identify the occupational origins of many cancers.

The cold fact is that since 1952 the successor organization which took over my work and which was directed from then on by individuals inexperienced and incompetent in this type of investi-

gation, has not published a single report on occupational cancers in industry.... As the result of these delaying and obstructing policies no cancer incidence data of any kind are available on the...large worker groups whose members have occupational contact with known or suspected cancer producing chemicals. (23)

Hueper's impatience and his penchant for controversy became something of a legend at the National Cancer Institute. His deeply felt sense of moral responsibility was ever evident. So was his brusque personality. These characteristics, coupled with a brilliant scientific mind which frequently put him years ahead of his colleagues in understanding the origins of human cancer, led to repeated confrontations. Dr. John R. Heller, Director of the National Cancer Institute during much of Hueper's tenure, recalls:

Bill was a teutonic individual who was usually right about what he said and what he did, but the way he was right was wrong. He had an uncanny facility for abrasiveness. Bill could get more people mad in a short period of time than most any man I have ever encountered.

I think it impaired his effectiveness. Bill had a way of publishing data without clearing it with anybody. He published in the Police Gazette, for example. I used to get called over to the Director's office to intercede, and he would say, "Why don't you fire that guy?" "On what grounds?" I would say. And he would say, "Well, he is causing so much trouble." I said, "Have you ever tried to fire anybody?" He said, "No." And I said, "I have no grounds to fire Bill. I have great respect for him and admiration for his work and I think he is contributing." But it was the way he went about it. He would come over to my office at least once a week and explode because somebody had been after him. And I would scrape him off the ceiling and send him back until the next week.

Bill was highly regarded professionally. I always found him to have good reasons for what he said and almost invariably he was right in what he said. If he said this was a carcinogen, then it was. But he just irritated the heck out of everybody. (24)

Dr. Thomas Marcuso, a protege of Dr. Hueper who first distinguished himself in the occupational carcinogenesis field with his post-World War II studies of lung cancer among chromate workers, recently commented at length regarding Dr. Hueper's contributions and his controversial personality.

You could sit with him by the hour and talk to him by the hour, and he would give you this tremendous scientific lift relative to the potential in the field. He is the one who oriented me in the field of occupational cancer. He was the one who provided me with the background so that I could develop my own insights.... He'd go over your data, as he did with my data, and he would recognize things, as for example he did when I was doing my asbestos study [in 1963]. I knew they [the cancer deaths] were there, but I didn't recognize the importance of the data that I had.... And the same with the chromate study. We worked together on that. You can see your work until you get up to a certain point. That was my first major effort.... [And] he gave it what I call the master's touch.

[H]e was a true scientist in his own right, and he had the intellectual capacity...he knew his scientific data even better than those who would try to oppose him.... Industry at that time realized of course that this was the first time that somebody who was really capable scientifically was coming onto the [occupational cancer] scene. (25)

Concerning Dr. Hueper's alleged belligerence, Dr. Mancuso observed:



If you and I are having a conversation and I'm wrong and you tell me, "Look, you are wrong on this thing; you've interpreted it incorrectly," does that mean that you are belligerent? That's all Dr. Hueper would do. He would not tolerate any nonsense; nor would he tolerate any lying on anybody's part, whether it was a scientist or an industry representative or a government representative.

When you believe what he so strongly believed-- that you have within the realm of science the potential for identifying occupational carcinogens and therefore preventing [cancer deaths, but don't], it's a disgrace. You could use stronger words than that: it's murder. (26)

Dr. Kenneth Endicott, former Director of the National Cancer Institute, summarized Hueper's contributions in these terms:

He [Hueper] would go after industry with a meat ax. He was ready to lower the boom on them before others would concede that the evidence was there.... But Hueper was a genius when it came to ferreting out carcinogenic agents. He really had a genius for that.... He's a great man. (27)

Hueper was not alone in his expressed frustration at retrogressive policies in the face of a growing occupational cancer menace. Writing in 1952, the eminent dermatologist, Dr. J. C. Downing stated:

The lack of investigation and early recognition of serious occupational hazards has impeded the progress of industrial medicine. It is apparent in the study and control of occupational health hazards...that the United States is not on a par with other countries. Lack of recognition of the importance of industrial skin cancer stands out in sharp contrast to the unrestricted and wide publicity given this important matter in England, Germany and Switzerland. The history of industrial medicine here is full of failures to prevent

the unnecessary deaths in industry that have occurred, for example, from berylliosis of the skin and lung, cancer of the lungs from chromates, tumors of the bladder due to aniline dyes, osteogenic tumors from radioactive chemicals, and cancer due to carcinogens in the tar industry. All these industrial hazards could have been controlled or eliminated. (28)

And in 1958, pointing to the abysmal funding levels for occupational health programs generally, Dr. Herbert K. Abrams wrote:

On the federal level the appropriation for 1958 for the Occupational Health program of the United States Public Health Service is only \$675,000--not enough to permit expansion of its already very limited program. On the state level at least nine states have no occupational health units in either their health or labor departments. All of the state agencies in this field, put together, have only 27 physicians employed. The United States Public Health Service in 1957 made the statement: "The services currently provided by these agencies within any one year can reach no more than 10 percent of the country's labor force." (29)

In 1964, at that time 70 years old and subject to mandatory retirement, Hueper co-authored with Conway a second massive text, this one entitled Chemical Carcinogenesis and Cancers. (30) In it he wrote ominously of an impending "epidemic in slow motion." He noted, emphasized, and then re-emphasized the fact that human cancer ordinarily does not appear until 10, 20 or even 30 or 40 years after effective exposure to a carcinogen. With this extraordinarily long latent period in mind, he warned that unless immediate and strict controls were applied, the unbridled proliferation of cancer-causing substances which accompanied the frenetic industrialization in the years since 1940 would, in time, produce a series of widespread cancer epidemics among countless categories of American industrial

workers. Policies of national neglect, joined with the passage of time, appear to be bearing out Hueper's prophecy.

. Rubber workers, routinely exposed to multiple cancer-causing substances, are dying of cancer of the stomach, cancer of the prostate, and leukemia and other cancers of the blood-and-lymph-forming tissues at rates ranging from 50 percent to 300 percent greater than in the general population. (31)

. Steelworkers, particularly the thousands who handle coal as it is transferred to coke ovens for combustion and distillation, fall victim to lung cancer at excessive rates. (32) Those who labor atop the hot coke ovens are most vulnerable to the carcinogenic coal tar emissions, dying from lung cancer at a rate seven times what would ordinarily be expected. (33)

. Workers who produce dyestuffs, using benzidine and other related chemicals, have evidenced notoriously high rates of bladder cancer. In a study of a group of dye workers who are exposed to benzidine and beta-Naphthylamine for five years or more, nearly all of them-- 94 percent--later developed bladder tumors. (34) The picture is nearly as depressing among certain groups of miners. Miners of uranium, (35) iron ore, (36) nickel, (37) chromium, (38) and other industrial metals succumb to a wide range of occupationally induced cancers. In the case of uranium miners, the lung cancer rate is extraordinary, accounting for upwards of 50 percent of all deaths among these workers. (39)

. An estimated two million workers, among them dry cleaners, painters, printers, and rubber and petroleum workers, are exposed

to the solvent benzene, a known leukemia-producing agent. (40)

. Another 1.5 million laborers, among them insecticide workers, farmworkers, and copper and lead smelter workers, are exposed to inorganic arsenic, a carcinogen which causes high rates of lung cancer and lymphatic cancer. (41)

. Meanwhile, machinists, chemical workers, woodworkers, roofers, and others join a rapidly expanding list of workers who hold jobs posing special cancer risks of one kind or another.

#### Asbestos: A Case Study in Occupational Carcinogenesis

Almost coincidental with Hueper's retirement in 1964 was the publication of convincing evidence regarding the identification of perhaps the most important of all occupational carcinogens: asbestos. While Dr. Irving Selikoff of New York's Mount Sinai Medical Center is generally credited with the pioneering work in this field, the asbestos-cancer link was first noted by Lynch and Smith in 1935, (42) and was documented further by British epidemiologist, Richard Doll, in 1955 (43) and by Breslow and others, also during the 1950s. (44, 45, 46) Interestingly, in 1963, one year before Selikoff published his findings, Dr. Thomas Mancuso sought to demonstrate how to conduct prospective, or cohort, industrial health studies by relying on data available from the Social Security Administration. (47) Although the emphasis of Mancuso's paper was on epidemiologic methodology, he illustrated the method's utility by applying it to the recorded health experience of workers in a local asbestos



company. The results pointed to the extraordinary cancer risk associated with exposure to asbestos fibers.

But it was Dr. Selikoff's 1964 publication, (48) and his subsequent attention to the need to popularize the significance of his findings, that prompted the current interest in the carcinogenic properties of asbestos. Working with the union locals of the International Association of Heat and Frost Insulators and Asbestos Workers, Selikoff and his associates, E. Cuyler Hammond of the American Cancer Society and Dr. Jacob Chung, obtained detailed work histories for a sample of 632 men who were on the union rolls as of December 31, 1942. Tracing them through 1962, they found that 45 died of cancer of the lung and pleura, whereas only 6.6 such deaths were expected. Selikoff wrote:

The results with regard to carcinoma of the lung are clear. Industrial exposure to asbestos of insulation workers, as studied here, results in a marked increase in the incidence of cancer of the lung, approximately six to seven times the expected incidence. (49)

Three of the pleural tumors were mesotheliomas; there was also one peritoneal mesothelioma. "Four mesotheliomas in a total of 255 deaths is an exceedingly high incidence for such a rare tumor." (50) In addition, Selikoff found that an unexpectedly large number of men died of cancer of the stomach, colon, or rectum (29 compared with 9.4 expected).

The implications of Selikoff's findings were critical. He had not only found an occupation--insulation work--involving an extraordinarily potent carcinogen; the carcinogen itself, asbestos, was

so widely utilized in industry--in shipbuilding, in construction, in the manufacture of brake linings, clutch facings, floor tiles, potholders and literally thousands of other commonly used products--that more than one million workers were estimated to be routinely placed at risk. (51)

A general recognition of the nature and potential extent of the asbestos-cancer link was at last being achieved. How was it that Selikoff was succeeding in communicating the import of his findings when similar findings, dating back decades, seemed to go unnoticed? There appear to be several explanations: First, Selikoff was attentive to the need to develop avenues of public communication; he made himself available to newspaper reporters, broadcast reporters, and in congressional hearings and other public forums. Second, Selikoff's work took place in the 1960s, during a period of American history when medical practitioners and others were increasingly encouraged to become public interest advocates; the Naderization of America seemed to invite the broadest public dissemination of scientific data of this kind. Third, related to these social conditions, a small number of labor leaders were finally becoming oriented to the chronic disease impact of specific working conditions. The traditional safety-oriented approach, relying on union bargaining power to gain "hazardous pay for hazardous work," was now being questioned by those who saw occupational health hazards as requiring governmental intervention if the conditions of employment were to be effectively improved.

The pervasive nature of the asbestos-cancer risk seemed in

itself an irrefutable argument for effective governmental regulatory action. But, in a sense, the asbestos findings served instead only to highlight the primitive state of occupational cancer control in the United States. From 1964, when Selikoff first published his asbestos-cancer findings, through 1971, no effective regulatory measures were taken by the federal government. In fact, with the exception of the Atomic Energy Commission's authority to regulate the manufacture and use of radioactive materials, there was no federal agency with authority to adopt nationally applicable regulations to control or otherwise limit occupational exposure to identified carcinogens. Occupational cancer control was left to the states where, in the main, industrial interests were well represented, and laxity prevailed in the occupational health field.

After years of struggle, with the 1970 congressional passage of the Occupational Safety and Health Act, (52) a federal framework was erected for the adoption and enforcement of nationwide occupational health standards, including national carcinogens standards. Health-conscious reformers reasonably believed that the Department of Labor's newly created agency, the Occupational Safety and Health Administration (OSHA), which was to administer the act, would give top priority to setting the toughest possible standards designed to protect workers against occupationally caused cancer. But OSHA's record as a fledgling agency only served to illustrate that the creation of federal legal authority in itself may not be enough to overcome institutional forces militating against effective controls.

In the case of asbestos (and other recognized carcinogens) OSHA was notably slow to adopt a national standard to control exposure levels. In fact, the agency failed to act on its own initiative and did not promulgate a final standard until June, 1972, (53) after the AFL-CIO's Industrial Union Department filed a legal petition compelling action under the Occupational Safety and Health Act.\*

The standard that OSHA ultimately adopted, reducing the allowable asbestos exposure by about half over a four-year period, was widely thought to be ineffective in addressing the demonstrated cancer hazard, having little, if any, impact upon incidence and mortality. (54)

Congressional funding for dissemination and enforcement of OSHA standards has been seriously deficient. The agency employs fewer than 2,000 compliance officers throughout the entire country. It is not surprising, then, that according to a Connecticut study, the majority of firms using asbestos in significant quantities have not even been effectively advised of what is required of management under the new asbestos standard. (55)

Given its recognized importance as a source of occupational cancer, the fact that governmental action to control asbestos exposure has, to date, been so ineffective does not augur well for occupational cancer control generally.

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\* In a footnote to the Watergate scandal, it was subsequently revealed that in 1972 George C. Guenther, then head of OSHA, had drafted a confidential memo to higher-ups in the Department of Labor promising a go-slow approach to the adoption of any standards generating controversy.



## Reflections on the History of Occupational Carcinogenesis

It wasn't until 1974 that OSHA finally adopted any further occupational health standards. As with asbestos, the standards it did adopt followed the filing of a petition to compel agency action. In this instance, the petition was filed by the Health Research Group, a Washington-based public interest law organization, which sought to force OSHA's regulation of 10 (later 14) recognized carcinogens. (56) Interestingly, among the substances included among the listed carcinogens were beta-Naphthylamine, benzidine, and other agents identified by Hueper and others decades before as potent cancer-causing chemicals. There appear to be several factors responsible for the inordinate lapse-time between discovery of a substance's occupational carcinogenicity and the regulation of that substance's manufacture and use.

. By its nature, occupational carcinogenesis involves findings which, if heeded, imply costly controls to corporate interests, thereby diminishing profitability. This economic factor has always been a powerful deterrent to the recognition of specific occupational cancer hazards. In addition, the scientific community's reluctance to embrace the value of cancer epidemiology, particularly in light of the difficulties of proof posed by a carcinogen's protracted latent period, further retarded progress in occupational cancer control.

. Prior to the passage of the federal Occupational Safety and Health Act of 1970, the traditional American approach to occupational cancer control had been to leave the matter to state regulation. In the context of state politics, the relative strength of industrial interests was so great as to make state-initiated occupational cancer control efforts exceedingly difficult.

. The potentially critical role which labor unions might have played in furthering occupational cancer control was never realized. An absence of effective leadership, coupled with a tendency to stress safety as opposed to health, minimized labor union contributions to preventive cancer control.

. Without a vocal constituency in the labor community, and in the face of opposition from affected corporate interests, scientists like Dr. Hueper tended to be isolated, their work in occupational carcinogenesis having far less impact on public policy than was merited. The kind of occupational cancer control advocacy which might have made a major difference in the Congress and elsewhere was not forthcoming from the National Cancer Institute. Indeed, when measured against the accumulating evidence on occupational carcinogenesis throughout the pre-World War II and post-World War II periods, occupational cancer control policy in the years since 1945 has been so slow in evolving and so lax in its implementation as to constitute a genuine national scandal.

Chronology of Significant Events in the History  
of Occupational Carcinogenesis

- 1775 Dr. Percival Pott noted the apparent relationship between scrotal cancer and exposure to coal soot among chimney sweeps.
- 1822 Dr. A. Paris observed the high incidence of skin cancer among workers exposed to inorganic arsenic.
- Late 1800s Dr. Ludwig Rehn and others noted the high incidence of bladder cancer among Central European dyestuffs workers.
- Early 1900s The cancer-causing properties of radioactive materials, including X-rays, were being generally recognized.
- 1914 Frederick L. Hoffman published The Mortality from Cancer Throughout the World, amassing statistical evidence pointing to the occupational and environmental origins of certain cancers.
- 1935 Lynch and Smith noted a link between occupational asbestos exposure and lung cancer.
- 1938 Dr. Wilhelm C. Hueper, through his experiments on dogs, conclusively identified beta-Naphthylamine as one of the aniline dyes responsible for human bladder cancer.
- 1942 Dr. Hueper published Occupational Tumors and Allied Diseases, identifying a series of specific occupational carcinogens.
- 1948 Dr. Hueper was appointed Chief of the National Cancer Institute's newly established Environmental Cancer Section in the Cancer Control Branch.
- 1952 Dr. Thomas Mancuso collaborated with Dr. Hueper in documenting an extraordinarily high incidence of lung cancer among American chromate workers.
- 1955 British epidemiologist, Richard Doll, and others further documented the link between occupational asbestos exposure and lung cancer.
- 1963 Dr. Mancuso, in illustrating a new approach to epidemiologic methodology, discovered anew the relationship between occupational exposure to asbestos and the subsequent high incidence of cancer.
- 1964 Dr. Irving Selikoff published his pioneering study, convincingly demonstrating the causative relationship between long-term asbestos exposure and a high incidence of lung cancer, both pleural and peritoneal mesothelioma, and cancers of the digestive tract.

- 1971     The Occupational Safety and Health Act of 1970 took effect, mandating the federal establishment and enforcement of nationwide occupational health and safety standards.
- 1972     OSHA promulgated a final standard for asbestos exposure, only after being legally petitioned to do so by labor organizations.
- 1974     OSHA promulgated a final standard for 14 carcinogens, only after being legally petitioned to do so by the Health Research Group (a Washington-based, Ralph Nader public interest organization).



Notes: Chapter 1

- (1) Pott, P.: Chirurgical Observations Relative to the Cataract, the Polypus of the Nose, the Cancer of the Scrotum, the Different Kinds of Ruptures, and the Mortification of the Toes and Feet. London, Hawes, Clarke, and Collins, 1775.
- (2) Hueper, W.C., Conway, W.D.: Chemical Carcinogenesis and Cancers. Springfield, Ill., Charles C. Thomas, 1964.
- (3) See note (2).
- (4) Hoffman, F.L.: The Mortality from Cancer Throughout the World. Neward, N.J., The Prudential Press, 1915, at 47.
- (5) Haagensen, C.D.: Am. J. Cancer 15: (part I)
- (6) Kennaway, E.L.: The occupational incidence of cancer of the penis and of the scrotum in the general population. Report, International Conference on Cancer. London, Bristol, John Wright & Sons, Ltd., 1928.
- (7) Interview with Dr. Wilhelm C. Hueper, research pathologist and author, by Larry Agran of HCCP, April 16, 1975, Fort Myers, Fla.
- (8) Hueper, W.C.: Occupational Tumors and Allied Diseases, Springfield, Ill., Charles C. Thomas, 1942.
- (9) See note (8) at 3-4.
- (10) Interview with Dr. Wilhelm C. Hueper, by Larry Agran of HCCP, December 18, 1975, Bethesda, Md.
- (11) Carcinogens standard. Department of Labor, OSHA. Federal Register, 39:3755-3797, January 29, 1974.
- (12) See note (10).
- (13) Rehn, L.: Blasengeschwülste bei Fuchsin-Arbeitern. Arch, klin. Chir. 50:588-600, 1895.
- (14) See note (10).
- (15) Hueper, W.C., Wiley F.H. Wolfe, H.D.: Experimental production of bladder tumors in dogs by administration of Beta-naphthylamine. Industrial Hygiene and Toxicology 20:369-377, 1938.
- (16) See note (10).
- (17) Auerbach, S.: N.J.'s chemical belt takes its toll. Washington Post. February 8, 1976, A1-A2.

- (18) See note (8) at 435-461.
- (19) See note (7).
- (20) Mancuso, T.F., Hueper, W.C.: Occupational cancer and other health hazards in a chromate plant: a medical appraisal, (I.) lung cancers in chromate workers. Industrial Medicine and Surgery 20:358-363, 1951.
- (21) Hueper, W.C.: Environmental cancer hazards. J. of Occup. Med. 14:149-153, 1972.
- (22) Hueper, W.C.: Organized labor and occupational cancer hazards. A speech prepared for delivery before the Executive Council of the AFL-CIO, 1959.
- (23) See note (22).
- (24) Interview with Dr. John R. Heller, by Devra Breslow of HCCP, November 4, 1975, Bethesda, Md.
- (25) Interview with Dr. Thomas Mancuso, by Larry Agran of HCCP, April 27, 1976, New York.
- (26) See note (25).
- (27) Interview with Dr. Kenneth Endicott, by Devra Breslow of HCCP, May 19, 1976, Rockville, Md.
- (28) Downing, J.G.: Cancer of the skin and occupational trauma. J.A.M.A. 148:245-252, 1952
- (29) Abrams, Herbert K.: Occupational health--the great hiatus. National Conference on Labor Health Services, June 16-17, 1958, at 113.
- (30) See note (2).
- (31) McMichael, A.J., et al.: Solvent exposure and leukemia among rubber workers; an epidemiologic study. J. Occup. Medi. 17:234-239, 1975
- (32) Lloyd J.W.: Long-term mortality study of steelworkers (part V., respiratory cancer in coke plant workers.) J. Occup. Med. 13:53-68, 1971.
- (33) See note (32).
- (34) Saffiotti, U.: The laboratory approach to the identification of environmental carcinogens. In Scholefield, P.G. (ed.): Proceedings of the Ninth Canadian Cancer Research Conference, vol. 9. Toronto, Univ. of Toronto Press, 1972, at 26.
- (35) See note (2).
- (36) See note (2).

- (37) See note (2).
- (38) See note (2).
- (39) See note (21).
- (40) Criteria for a recommended standard: occupational exposure to benzene. National Institute for Occupational Safety and Health, U.S. Dept. of HEW.
- (41) Criteria for a recommended standard: occupational exposure to inorganic arsenic. National Institute for Occupational Safety and Health, U.S. Dept. of HEW.
- (42) Lynch, K.M., Smith, W.A.: Pulmonary asbestosis: carcinoma of the lung in asbesto-silicosis. Am. J. Cancer 24:56-64, 1935.
- (43) Doll, R.: Mortality from lung cancer in asbestos workers. Brit. J. Indust. Med. 12:81-86, 1955.
- (44) Breslow, L., Hoaglin, L., Rasmussen, G., et al: Occupations and cigarette smoking as factors in lung cancer. Am. J. Pub. Health
- (45) Breslow, L.: Industrial aspects of bronchiogenic neoplasms. Dis. of the Chest 28:421, 1955.
- (46) Dunn, J., Linden, G., Breslow, L: Lung cancer mortality experience in men in certain occupations in California. Am. J. Pub. Health 50:1475, 1960.
- (47) Mancuso, T.F., Coulter, E.J.: Methodology in industrial health studies. Arch. of Environ. Health 6:210-226, 1963.
- (48) Selikoff, I., et al: Asbestos exposure and neoplasia. J.A.M.A. 188:22-26, 1964.
- (49) See note (48).
- (50) See note (48).
- (51) Taylor, G.H.R. (Executive Secretary, AFL-CIO Standing Committee on Safety and Occupational Health): letter to James D. Hodgeon, Secretary of Labor, November 4, 1971.
- (52) Occupational Safety and Health Act of 1970 (29 U.S.C. 655).
- (53) Occupational safety and health standards: standard for exposure to asbestos dust. Federal Register 37:11318-11322.
- (54) Brodeur, P.: The Expendable Americans. New York, Viking, 1974.
- (55) Schoenberg, J.B., Mitchell, C.A.: Implementation of the federal asbestos standard in Connecticut. J. Occup. Med. 16:781-784, 1974.
- (56) See note (11).





## CHAPTER 2

### CARCINOGENESIS BIOASSAYS

#### The Curious Relationship

In drawing upon both epidemiological studies and animal studies in writing his now famous classic, Occupational Tumors and Allied Diseases, Dr. Hueper implicitly documented the curious relationship that existed between cancer epidemiology and the use of bioassays to determine a substance's carcinogenic properties. Until the early 1940s, animal testing was used only to confirm the carcinogenicity of a substance after its cancer-causing effects had already become evident in man. Hueper's own work with bladder cancer was a case in point: Dr. Ludwig Rehn first observed cases of bladder cancer among dye workers in Germany in 1895. Yet it wasn't until 43 years later--in 1938--that Hueper reproduced the same kinds of bladder cancers in dogs through his experiments with beta-Naphthylamine. (1) With other carcinogens--among them X-rays, chromates, asbestos, and coal tars--the pattern was invariably the same: The first evidence of carcinogenicity was gleaned from humans; animal testing followed for purposes of confirmation.

It was not until 1940 that this pattern was reversed, at first by accident and then later by design. In 1940, American researchers were testing the effects of a new insecticide, 2-Acetylaminofluorene, or 2-FAA, when they inadvertently discovered that the chemical induced

several types of tumors in rats. Through this routine procedure to determine toxic impact, scientists found the insecticide to be unfit for use in the human environment, and its commercial use was barred by the Department of Agriculture. (2) A similar history characterizes the discovery of the effects of urethane. In 1943, the chemical was utilized as an anesthetic for mice in radiation experiments conducted at the National Cancer Institute. Surprisingly, pulmonary tumors proliferated in the rodents, and the carcinogenic effect of urethane was discovered as an accidental by-product of the radiation experiments. (3)

Even as late as 1950, there appears to have been scant recognition of the value of systematic animal testing as an indicator of cancer hazards to be avoided by man. Why? The scientific techniques were available. Indeed, by this time bioassays for carcinogenic properties were sufficiently sophisticated to be of great benefit in safeguarding the public against cancer-causing substances. (4) Why, then, was the predictive potential of animal testing so slow to be exploited? Dr. Umberto Saffiotti, Associate Director of NCI's Carcinogenesis Program from 1968 to 1976, offers a twofold explanation: First, there was the matter of inertia--the kind of inaction which frequently accompanies a scientific advance, particularly an advance which has no marketable value in the private sector. And, second, there was the peculiarly unappealing nature of animal testing. To many, the work appeared to be intellectually barren: painting or injecting or feeding rodents, and maintaining the animals for periods of up to several years before measuring the carcinogenic response by counting tumors. (5)

## The Delaney Amendment

It wasn't until 1956 that the prophylactic utilization of carcinogenesis bioassays was given new impetus. Meeting in Rome, the International Union Against Cancer (IUCC) assembled a panel of medical authorities from throughout the world to discuss potential cancer hazards posed by chemical additives and contaminants in food. The participants recognized the "urgent necessity for international collaboration for the protection of mankind" against cancer. (6) At its conclusion, the IUCC conference unanimously adopted a recommendation calling for the long-term pre-testing of food additives in animal species. (7) The conference stated further: "Any substance which. . .when tested [in animals], is shown conclusively to be a carcinogen at any dosage level, for any species of animal, following administration by any route, should not be considered innocuous for human consumption." (8)

The Rome statement came at a propitious moment with respect to its impact upon legislative policy in the United States. New York Congressman James J. Delaney, who in the early 1950s had unsuccessfully introduced a major food additives control bill, formulated and introduced another bill in May of 1957. In it, he incorporated the recommendations of the IUCC conference. The controversial anti-carcinogen provision, which soon became known as the Delaney Clause, (9) legislatively embodied the scientific conclusions unanimously agreed upon by the world's leading cancer researchers: No food additive could be approved for human consumption by the Food and Drug Administration if it was found to induce cancer in man or animals. Delaney explained his reason for adding the clause in the simplest of terms.

So far as medicine is concerned, I make no pretense to any special knowledge. I felt that the recommendation of so many experts, both in countries abroad as well as in the United States, should not be disregarded. Accordingly, I amended [the bill] to include an anti-carcinogen provision. . . . (10)

Dr. P. F. Hopper, Director of Nutrition and Health Sciences for General Foods Corporation and an opponent of the Delaney Clause, offered a different perspective concerning the clause's adoption.

The emotional aspects of "tampering" with our food supply and the fear that is conjured up by the word "cancer" [make] it easy to see why the Delaney Clause achieved its place in the sun. (11)

In the nearly two decades since its passage, the Delaney Clause has generated enormous controversy. (12) The FDA, charged with administering the clause, has never been enthusiastic about its provisions. In 1969, then-Secretary of Health, Education, and Welfare, Robert Finch, announced the banning of cyclamates because they were found to induce bladder cancer in test animals. In announcing the ban which affected an estimated \$1 billion per year in food products, Finch stated almost regretfully, "I have acted under the provisions of the law because. . . I am required to do so." (13) The cyclamate episode, plus the clause's purported deterrent effect--discouraging the development and promotion of still more food additives--have prompted Congressman Delaney to assert that the clause ". . . has saved millions of people from suffering." (14)

Whatever the final judgment, the clause is far from secure as a legislative expression of cancer control policy. In 1973, Dr. Samuel Epstein, then Professor of Environmental Health and Human Ecology at Case Western Reserve Medical School, offered these comments regarding threats to the Delaney Clause.



For the third time since its passage in 1958, the Delaney Amendment to the Federal Food, Drug, and Cosmetic Act is again under attack. In hearings on the hazards of color additives in 1960, in the wake of the cyclamate ban in 1969, and now after the partial ban of DES in 1972, the Delaney "Anti-cancer" clause has been subjected to vigorous attack by those who claim its strict prohibition against the deliberate addition of chemical carcinogens to food is too rigid and arbitrary. In each of these three instances, the food and chemical industry has sounded alarms that the clause, if continuingly enforced, will substantially hamper production of food by modern scientific technology....

It is perhaps no coincidence that the attacks on the Delaney Amendment are occurring at a time when the food chemical industry is poised for a major expansion. The chemical industry predicts that sales of chemical additives are expected to grow from \$485 million in 1970 to \$750 million by 1980. (15)

### Carcinogenesis Bioassays and Public Policy

Beyond the narrow question of special interest attacks on the Delaney Clause there lies the broader struggle over how to use carcinogenesis bioassays in shaping public policy. Dr. Saffiotti and others have felt the necessity to state and restate the scientific underpinning for animal pre-testing, not only in the realm of food additives but in other areas as well.

Several individual chemicals or mixtures of chemicals have...been shown conclusively to be carcinogenic by direct observation in man. With the exception of arsenic, still under experimental study, all the main products that were found to be carcinogenic by direct evidence in man have also been proven carcinogenic in animals. On the other hand, proof that a substance, which had been recognized as carcinogenic in animals, actually causes cancer in man would require in most cases extremely complex and lengthy epidemiologic studies. In many cases, it may be impossible to obtain such proof because of the complexity of controls that would be needed for a satisfactory demonstration. Therefore, the only prudent course of action at the present state of our knowledge is to assume that chemicals which are car-



cinogenic in animals could also be so in man, although the direct demonstration in man is lacking. (16)

Or, in the words of former HEW Secretary Arthur Flemming:

Scientifically, there is no way to determine a safe level [for humans] for a substance known to produce cancer in animals. . . . (17)

In effect, Flemming and Saffiotti have argued that the Delaney Clause is a carefully drawn reflection of the state of the art relative to carcinogenesis bioassays. On one hand, the techniques are sufficiently advanced to render carcinogenesis bioassays important indicators of potential cancer hazards; yet, on the other hand, once a substance is demonstrated to cause cancer in test animals, there is no current scientific basis for determining a "safe level" of exposure to humans if, indeed, there is such a thing as a "safe level" of exposure to a carcinogen.

Historically, the Delaney Clause--limited to food additives--has been the prototypical lightning rod in what is really a vast controversy over a national carcinogens policy ultimately addressed not just to food additives, but also to occupational carcinogens, carcinogenic pesticides, and the control of carcinogens in the air, water, and in products destined for household use. There have been those like Saffiotti who have pointed out the current limits of carcinogenesis bioassays and have argued the need for prudent policies in light of these limits. And, on the opposite side, there have been those who have insisted upon more conclusive proof of carcinogenicity in man and have stood against regulatory restraints in the absence of such proof. (18) Caught in the midst of this highly politicized controversy, throughout the 1960s and into the 1970s federal regulatory agencies have been ex-

ceedingly slow to recognize the value--and the inherent limitations--of carcinogenesis bioassays. It wasn't until 1974 that the Environmental Protection Agency relied expressly and unhesitatingly upon animal data to ban two pesticides, aldrin and dieldrin, as posing an unreasonable risk of cancer to humans even though human carcinogenicity could not yet be proved. (19) This decision was in sharp contrast with the agency's 1972 decision to ban DDT, a decision which reflected a reluctance to draw conclusions based upon three-year-old animal tests that demonstrated the carcinogenicity of the pesticide. (20)

Within the National Cancer Institute itself, under Dr. Saffiotti's leadership, the Carcinogenesis Program emerged as the Institute's most politically troubled unit. How much carcinogenesis testing should be undertaken? What substances, affecting which commercial interests, should be tested? How should the results be interpreted and utilized? Dr. Saffiotti's 1976 resignation as Associate Director of the Carcinogenesis Program was attributable largely to his view that the Institute was failing in its obligation to properly support carcinogenesis. In his annual report for fiscal year 1973, Saffiotti wrote openly of his distress at the lack of financial and political support for the Carcinogenesis Program.

I submit that the subject of the Carcinogenesis Program is of the greatest importance for the ultimate control of cancer in man. As repeatedly stated, a complex program requiring the intimate interaction of many key scientific methodologies cannot be accomplished without a scientific staff of the first order. A freeze on hiring and a cutback in personnel ceiling has hit the Program in the middle of an expansion of activities that it had been urged to undertake; this has determined a situation where three of the most distinguished scientists and program leaders have decided to leave their positions on the Carcinogenesis staff. . . .

Our present inability to fill. . .technical positions could bring to a complete stop the activity of some of the most fruitful areas of research in our Program. I question our ability to retain much longer in the Program the scientists so affected, when all credibility about the Institute's intent of developing and supporting national programs of high scientific value would be lost. (21)

Saffiotti continued:

Major advisory responsibility is requested [of the Carcinogenesis Program] from large groups of industries, from consumer protection agencies and from labor unions. Clearly major national interests are at stake. Yet within the NCI, the Carcinogenesis Program does not even have Division status and more importantly the Program is not even directly represented in the NCI's Executive Committee, which is thus deprived of expertise in this area of vast national concern. The Program's director has not even had the opportunity of close access to the Director of NCI....[T]he lack of direct involvement of the Institute's leadership and of its national advisory bodies in the Carcinogenesis Program's activities has caused considerable discouragement to its staff. (22)

When Dr. Saffiotti resigned his post in the spring of 1976, he insisted that the denial of adequate support to the bioassay portion of the Carcinogenesis Program had led to lengthy delays in analyzing and publishing test results. (23) In a subsequent letter sent to Senator Edward Kennedy, then-NCI Director Frank Rauscher, Jr. affirmed the National Cancer Program's commitment to the Carcinogenesis Program. But Rauscher's letter indicated the acutely politicized context of the Saffiotti controversy and of the Carcinogenesis Program itself.

Dr. Saffiotti. . .belongs to the academic tradition, and he found it difficult to cope with the new demands of the National Cancer Program, and particularly with the need to provide a truly national forum where all interested voices could be heard, where decisions could be made after a broad base of opinion had been rendered, and where the function of the government would be not that of a contending advocate but rather of policy making in the national interest. (24)



Two recent developments--one scientific and one legislative--appear destined to add to the political pressures to develop a clear, coherent national carcinogens policy. In the scientific sphere, an important advance will now make it possible to be much more efficient in screening chemical and physical agents than has historically been the case. The Ames test, named after its developer, Professor Bruce Ames of the University of California at Berkeley, provides a cheap and quick indication of a chemical's cancer-causing potential by its observed effect on bacteria. Requiring only a few days to perform, this in vitro test is based on the fact that nearly all chemicals that cause cancer in animals and man also produce mutations in bacterial cultures. (25) Accordingly, agents found to be mutagenic in bacteria should ordinarily be regarded as suspect carcinogens.

Apart from this scientific development, the Congress in 1976 passed the Toxic Substances Control Act. The measure, which was given impetus by the established connection between vinyl chloride and a series of resulting worker deaths from angiosarcoma of the liver, extends broad authority to the Administrator of the Environmental Protection Agency to require companies to undertake pre-market testing of chemicals to establish their carcinogenic or other harmful properties. (26)

With the advent of the Ames test, and with the mandate of the Toxic Substances Control Act, the extent of carcinogenesis testing appears certain to accelerate in the years immediately ahead. Still unresolved, however, except with respect to the limited application of the Delaney Clause to food additives, is the fundamental question: If a substance is tested and revealed to be a carcinogen, what public policy will follow?

Chronology of Significant Events in the History  
of Carcinogenesis Bioassays

- 1938 Dr. Wilhelm C. Hueper produced bladder cancer in dogs by injecting them with beta-Naphthylamine.
- 1940 Researchers inadvertently discovered that 2-Acetylaminofluorene produced tumors in rats.
- 1943 Researchers inadvertently found that urethane caused pulmonary tumors in rodents.
- 1956 An assembled conference of the International Union Against Cancer issued a statement calling for long-term pre-testing of food additives in animal species.
- 1958 The Delaney "Anti-cancer" Clause became law, requiring the FDA banning of food additives found to cause cancer in animal tests.
- 1969 HEW Secretary Finch announced the banning of cyclamates.
- 1972 The Environmental Protection Agency banned most uses of DDT, but without relying on animal tests demonstrating the pesticide's carcinogenicity.
- 1974 The EPA banned the pesticides aldrin and dieldrin, for the first time relying exclusively upon animal data of carcinogenicity.
- 1976 Dr. Umberto Saffiotto, Associate Director in charge of NCI's Carcinogenesis Program, resigned in protest over carcinogenesis policy.
- 1976 The Ames test, a quick in vitro method of carcinogenesis testing, began to be widely used.
- 1976 Congress passed, and the President signed into law, the Toxic Substances Control Act.



Notes: Chapter 2

- (1) Hueper, W.C.: Experimental production of bladder tumors in dogs by administration of Beta-naphthylamine. J. Indust. Hygiene 20:46-84, 1938.
- (2) Shimkin, M.B., Triolo, V.A.: History of chemical carcinogenesis: some prospective remarks. The International Symposium on Carcinogenesis and Carcinogen Testing, Boston, Massachusetts, 1967. Prog. in Exp. Tumor Res. 11:1-20, 1969.
- (3) See note (2) at 12-13.
- (4) Interview with Dr. Wilhelm C. Hueper, former Chief of the Environmental Cancer Section of the National Cancer Institute, by Larry Agran of HCCP, December 19, 1975, Bethesda, Md.
- (5) Interview with Dr. Umberto Saffiotti, former Associate Director of the Carcinogenesis Program of the National Cancer Institute, by Larry Agran of HCCP, December, 1975, Bethesda, Md.
- (6) IUCC: Report of Symposium on Potential Cancer Hazards from Chemical Additives and Contaminants to Foodstuffs. Acta Vol. XIII.
- (7) See note (6).
- (8) See note (6).
- (9) Food, Drug, and Cosmetic Act. 21 U.S.C. 348(c)(3)(A).
- (10) Congressional Record (House) 17420, August 13, 1958.
- (11) Hopper, P.F.: The Delaney Clause. Prev. Med. 2:159-160, 1973.
- (12) Wynder, E.L. (ed.): The Delaney Clause Controversy. Prev. Med. 1:123-170, 1973.
- (13) Turner, J.S.: The Chemical Feast. New York, Grossman, 1970.
- (14) See note (13).
- (15) See note (12) at 140 and 148.
- (16) Saffiotti, U.: The Laboratory Approach to the Identification of Environmental Carcinogens. In Scholefield, P.G. (ed.): Proceedings of the Ninth Canadian Cancer Research Conference, Vol. 9. Toronto, University of Toronto Press, 1972, 23-36, at 23.

- (17) See note (12) at 141.
- (18) See note (12).
- (19) Shell Chemical Co. et al: Consolidated Aldrin/Dieldrin Hearing.  
Federal Register 39:37216-37272, October 18, 1974.
- (20) Environmental Protection Agency: Consolidated DDT Hearings.  
Federal Register 37:13369-13376, July 7, 1972.
- (21) Report of the Carcinogenesis Program, Fiscal Year 1973.  
Division of Cancer Cause and Prevention, National Cancer  
Institute, U.S. Dept. of HEW, 42-43.
- (22) See note (21) at 45.
- (23) Rauscher Responds to Saffiotti's Charges in Letter to Sen.  
Kennedy. The Cancer Letter, Vol. 2, No. 24, pp. 3-5.
- (24) See note (23).
- (25) McCann, J., et al.: Detection of carcinogens as mutagens.  
Proc. Nat. Acad. Sci. 72:5135-5139, 1975.
- (26) Toxic Substances Control Act of 1976.

## CHAPTER 3

### TOBACCOGENIC CANCER

#### Introduction

In 1919, when Alton Ochsner was a junior in medical school at Washington University in St. Louis, a patient with cancer of the lung was admitted to Barnes Hospital, the teaching hospital for Washington University. In a short time, the patient died. Ochsner recalled the incident:

Dr. George Dock, who was an eminent clinician and pathologist, asked the two senior classes to witness the autopsy because, as he succinctly said, the condition was so rare he thought we might never see another case as long as we lived. Being very young at the time and enamored by the clinical knowledge and judgment of our eminent professor of medicine, I was greatly impressed by this extremely rare condition. (1)

When Ochsner recorded these recollections in 1973, he was 77 years of age. Lung cancer--a condition "so rare. . .we might never see another case as long as we lived"--had, in fact, become a modern epidemic of massive proportions. The disease currently kills upwards of 83,000 Americans each year; in 1976 an estimated 65,200 men and 18,600 women died from the disease. (2) As a result of perhaps the most important

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\* Principal Researcher/Writer: Larry Agran

twentieth century advance in carcinogenesis, it is now stated with confidence that approximately 80 percent of all lung cancer deaths in the United States are caused by cigarette smoking. (3)

### The Early Evidence

After graduating from medical school, Alton Ochsner went on to become a surgeon and an early leader in lung cancer surgery. He was also among the earliest scientists to explore the relationship between cancer of the lung and the use of tobacco.

Seventeen years elapsed before I saw another case of lung cancer, at the Charity Hospital in New Orleans after having come to Tulane University as Professor of Surgery in 1927. There was nothing particularly unusual about seeing a rare case in 17 years, but eight other additional cases were seen in a period of six months which was extremely unusual. Having been impressed with the extreme rarity of the condition 17 years previously, the sudden increase in incidence represented an epidemic, and there had to be some reason for it. All the patients involved were men; they all smoked cigarettes heavily and had begun smoking in the First World War. I then ascertained that very few cigarettes were consumed before the First World War but during the war and afterward there had been a tremendous increase. Since there was a parallel in the rise in sale of cigarettes and the appearance of the new disease with a lag of approximately 20 years from 1914 to 1936, I considered that this might be the necessary length of time for a possible carcinogenic agent in tobacco smoke to become evident. The evidence was admittedly very nebulous, but it seemed as if this was the most likely cause. (4)

European studies, most notably that of Müller in Germany in 1939, (5) began to show a strong statistical association between lung cancer and smoking. Two years later, in 1941, Ochsner joined with Michael DeBakey in publishing the first American study to stress the cigarette-lung cancer connection. (6) Based on clinical observations of autopsies performed in the United States and in other countries, these researchers found that the incidence of pulmonary carcinoma had doubled over the 18-year period studied, "whereas the increase in the incidence of all carcinoma in all



autopsies was relatively slight." (7) Noting the parallel increase in cigarette sales over the same period, the study concluded, "It is our definite conviction that the increase of pulmonary carcinoma is due largely to the increase in smoking, particularly cigarette smoking, which is universally associated with inhalation." (8)

Dr. Michael Shimkin has written of epidemiologists in these terms:

Epidemiologists are a mixed lot and come from many walks of medical, sociological, and economic persuasions. They include statisticians who refuse to be browbeaten by clinicians, physicians who acquire a nodding acquaintance with statistics, and geographic pathologists who learn to distinguish pathology specimens from people. There are also macroepidemiologists, who consider it beneath their dignity to deal with populations of less than 100,000, and microepidemiologists, who look for intuitive insights in unusual small clinical experiences. (9)

Intuition. Pathology. Statistics. Each was important as the cigarette controversy emerged as the leading field in cancer epidemiology shortly after World War II. Interestingly, amid an atmosphere conducive to scientific inquiry, Washington University contributed more than its fair share of prominent personalities to the fray. Of course, Alton Ochsner was himself a product of Washington University. But there were others. Dr. Evarts Graham, who in 1933 performed the first successful pneumonectomy for cancer of the lung, was Ochsner's professor of surgery in his senior year. Some years after his graduation, when Ochsner first postulated that the increase in lung cancer was due to cigarette smoking because of the parallel between the sale of cigarettes and the increasing incidence of the disease, he was chided by Graham. Graham, who was a very heavy cigarette smoker, said, "Yes, there is a parallel between the sale of cigarettes and the incidence of cancer of the lung, but there is also a parallel between the sale of nylon stockings and the incidence of cancer of the lung." (10) Ochsner recalled further:



A few years later Dr. Graham wrote to me and reminded me [of the incident] and said that he would have to "eat crow" because a young man, a sophomore student at Washington University, had taken his [Dr. Graham's] cases of cancer of the lung and studied them and the results of this study convinced Dr. Graham that there was a relationship between cigarette smoking and cancer of the lung. This young sophomore student was Ernst Wynder. . . . (11)

In 1950, Graham and Wynder together published the results of their epidemiological study. (12) In their investigation, they employed a retrospective method of study: They interviewed patients already known to have lung cancer and, inquiring about their smoking habits, they then compared these responses to the responses of patients without lung cancer. The results indicated that proportionately more heavy smokers were found among the lung cancer patients than the control group population; fewer light and non-smokers were found among the cancer patients than among the controls. Graham and Wynder concluded: "Extensive and prolonged use of tobacco, especially cigarettes, seems to be an important factor in the inducement of bronchogenic carcinoma." (13)

Persuaded by the evidence, Graham altered his personal smoking habits, decreasing his cigarette consumption to six per day--two after each meal. Then, in 1953, when Graham and Wynder were able to prove that the tar from cigarette smoke when applied to the surface of animals produced skin cancer, (14) Graham quit smoking altogether. But it was too late. A few years later he wrote to Alton Ochsner, "Because of our long friendship, you will be interested in knowing that they found that I have cancer in both my lungs. As you know, I stopped smoking several years ago but after having smoked as much as I did for so many years, too much damage had been done." (15) Wynder recalled the tragic irony of Graham's death.

When he was dying I went to St. Louis. He was laying [sic] in an oxygen tent. I remember he pointed to a little sign on the oxygen tent where it said "No Smoking." He said, "I should have listened." He wrote me a very moving letter stating that fate had really done him badly for all the work he had done on lung cancer. (16)

On March 4, 1957, Dr. Evarts Graham, the first person to surgically remove a human lung, was himself dead from lung cancer.

Important as it was as an epidemiological study, the Wynder-Graham investigation was but the beginning of a great mid-century scientific debate. Serious questions remained, not the least of them directed to the techniques employed in the Wynder-Graham study itself. The questions were raised not only by the tobacco interests that were obviously threatened by the study's conclusions, but also by scientists of considerable reputation. Dr. Lester Breslow, currently Dean of the School of Public Health at UCLA, was a state public health epidemiologist in California in the late 1940s when he first encountered Ernst Wynder at work on the Wynder-Graham study.

About 1947-48--in that period--we were visited in Berkeley by a medical student named Ernst Wynder. He came in with an obviously very strong conviction that cigarette smoking was a factor in lung cancer. Wynder had undertaken what we later began to call a retrospective or case control study of the matter. He came by to let us know that he was going to be visiting the hospitals in the Bay Area to interview patients and controls in regard to their smoking practices.

We thought he was a pretty brash young man. . .and asked whether a member of our staff, named Hoaglin, could accompany him around to the hospitals just to see what he was doing. Hoaglin came back with a horrible story of poor technique, a very sloppy approach to the interviewing. And so we decided we ought to do a proper kind of study. We were quite astonished with the results, which were almost identical with those Wynder was obtaining by what had appeared to us as very biased and sloppy techniques. (17)

It was this remarkable similarity of results that made early converts of Breslow and others. But still more was needed before a consensus among scientists would emerge on the matter. Breslow's early

work, (18) like Ochsner's and Graham and Wynder's, was a retrospective study with all its attendant problems. According to Breslow:

It seemed to me that the retrospective approach to the matter--the case control studies--were vulnerable methodologically on the grounds of bias of samples. The people already had the disease; they were selected people who were being interviewed; and it is very difficult, if not impossible, to get perfect controls. You depend upon what the patient recollects and is willing to tell you and the accuracy of what he says about his smoking habits. There were a lot of reasons why one could doubt the significance of these retrospective studies. The issue was only going to be resolved by what we later came to call prospective studies. (19)

### The Emerging Consensus

Soon after the Wynder-Graham study was published in 1950, a number of prospective studies were organized throughout the country. The prospective method examines the smoking habits of a sizeable population--apparently healthy--and then follows that group over a period of years in which the rates and causes of mortality are recorded. In this way, the problems of retrospective falsification or the failure of memory or the selection of improper controls are avoided. The most influential prospective study in the United States was that undertaken by Drs. E. Cuyler Hammond and Daniel Horn. (20) With the assistance of American Cancer Society volunteers, Hammond and Horn tracked 187,783 American men to determine what effect, if any, smoking habits had upon mortality. The results, published in the Journal of the American Medical Association in March, 1958, (21) confirmed the findings of the retrospective studies. In fact, all of the prospective studies of the late 1950s--including the 1956 study of British doctors by Doll and Hill (22) and the 1959 Dorn study of 200,000 U.S. war veterans with government life insurance policies--(23) showed that the total death rate for cigarette smokers was



approximately 70 percent higher than that for non-smokers. Lung cancers, and cancers of other sites, accounted for a disproportionately high number of the excess deaths. In all of the studies, as the amount of cigarette consumption increased, so did total mortality rates. In terms of public health policy, an especially significant finding in the Hammond-Horn investigation was that the mortality risk from smoking decreased as the number of years of smoking cessation increased. (24)

By the mid-1950s, dispute among scientists investigating the cigarette-cancer connection was waning. A consensus on the causal connection was clearly taking shape. The cigarette, first described as possibly "associated" with lung cancer and, later, as a "factor" in the disease, was now described with increasing confidence as the overriding cause of the twentieth century lung cancer epidemic. In fact, in this period of rapidly mounting scientific evidence, Surgeon General Leroy Burney, urged by NCI's Dr. Michael Shimkin, had a statement prepared in 1957 concerning the cigarette-lung cancer connection. For well over 2 years, Dr. Burney's statement remained mired in the federal health bureaucracy, subject to countless revisions and clearances. (See Book Two, Chapter 5.)

It wasn't until November, 1959, that the statement was finally published--as an article in the Journal of the American Medical Association. (25) Entitled "Smoking and Lung Cancer: A Statement of the Public Health Service," the article declared: "The weight of evidence...implicates smoking as the principal etiological factor in the increasing incidence of lung cancer." (26) Interestingly, the Surgeon General's statement received little publicity; and its overall impact on public policy was negligible.

In 1962, the Royal College of Physicians in London stated their conclusion on smoking and cancer causation in the plainest of terms: "The strong statistical association between smoking, especially of cigarettes, and lung cancer is most simply explained on a causal basis." (27) The report of the Royal College of Physicians went on to raise the spectre of a second stage in the lung cancer epidemic--the toll it was yet to take among women. Because women did not develop smoking habits quantitatively comparable to those of men until after World War II, it was hypothesized that the full effect of cigarettes on the female lung cancer rate could not be assessed for some years, in view of the time period ordinarily required before cancer manifests itself.

#### The Surgeon General's Report on Smoking and Health

In January, 1964, two years after the Royal College of Physicians' report, the Surgeon General's Advisory Committee on Smoking and Health published what was to become the definitive American statement. (28) In arriving at its conclusions on the effects of smoking, the committee experts evaluated three kinds of scientific evidence: (1) animal studies in which the effects of smoke, tars, and toxic irritants were measured; (2) clinical and autopsy studies of smokers and non-smokers, such as the Ochsner-DeBakey study; and (3) epidemiological studies, both retrospective and prospective. Second only to its impact on the smoking-health controversy, perhaps the most critical contribution of the Advisory Committee's report was to gain lasting acceptance for epidemiology as a bona fide science that could no longer be dismissed as "mere statistics." While epidemiology had been recognized for some time as useful in the study of acute disease, the 1964 Surgeon General's report established epidemiology's



utility for the investigation of chronic diseases, such as cancer.

Chapter 9 of the Advisory Committee's report was titled simply "Cancer." The chapter's 136 pages consisted of an exhaustive review of the epidemiological evidence not only with respect to tobaccogenic lung cancer, but for other organ sites as well, such as the mouth, larynx, esophagus, urinary bladder, and stomach; other chapters in the report reviewed epidemiological evidence linking cigarettes to non-neoplastic respiratory diseases, cardiovascular diseases, and other conditions. Dealing directly with the question of ascribing causation based on a statistical association between a factor such as cigarette smoking and a disease such as lung cancer, the Committee wrote:

Causal Significance of the Association. -- As already stated, statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between cigarette smoking and lung cancer a number of criteria must be utilized, no one of which by itself is pathognomonic or a sine qua non for judgment. These criteria include:

- (a) The consistency of the association
- (b) The strength of the association
- (c) The specificity of the association
- (d) The temporal relationship of the association
- (e) The coherence of the association (29)

Employing these criteria, the Committee concluded that:

1. Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.
2. The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking. (30)

While making no specific policy proposals, the report went on to call for "remedial action" to reduce the health hazard posed by cigarette smoking.

Viewed historically, it is now apparent that the report had the remarkable effect of really settling the scientific issue whether cigarettes indeed caused lung cancer. How was it that this second Surgeon General's report proved so effective when the Burney report--initiated in 1957 and published in 1959--had been so ineffective? Several reasons emerge. First, the passage of time itself was a key factor. Between 1957 and 1964, the findings of some of the large prospective epidemiologic studies were being published, confirming earlier work, and solidifying the growing scientific consensus on tobaccogenic cancer.

Second, in both its design and scope, the 1964 report was a far more impressive document. Employing a sizeable staff, the Advisory Committee took more than a year to exhaustively review virtually all of the evidence at hand regarding the smoking-health issue generally, and the cigarette-cancer issue specifically. The full document, almost 400 pages long, reflected the kind of care that would enable the report to withstand the scrutiny and criticism that would inevitably follow its release.

The third reason for the effectiveness of the 1964 report, as compared with the 1959 Burney report, can be attributed to what might be called the managerial factor. From beginning to end, Surgeon General Luther Terry sought to assure maximum impact of the report's findings---whatever they might be. The report was not to be his per se, but rather the report of an "expert committee," acknowledged by the President, thereby gaining enormous stature. (31) Dr. Terry selected the 10-member Advisory Committee in a way to virtually guarantee that there would be no subsequent charges of bias. He insisted that no one could be a member of the Advisory Committee if he had been publicly identified with any

position on the smoking-health question. (32) Moreover, he astutely allowed the Tobacco Institute to veto any proposed nominees to the Advisory Committee. (33) In this way, the Surgeon General managed to bestow upon the Advisory Committee the tobacco industry's implicit endorsement as to its objectivity. Throughout the investigation, all meetings and staff work were conducted in a politically protected environment, based at the National Library of Medicine. (34) Dr. Terry forbade the Committee members to speak to politicians or the press. In exchange, he secured assurances from President Kennedy and HEW Secretary Ribicoff (and, later, Anthony Celebrezze) that the Committee could carry out its work insulated from any political influence. (35) Consistent with these precautions, there were no leaks or any other disclosures to sap the final report of its desired impact. Finally, when Dr. Terry released the report on January 11, 1964, it was with the utmost fanfare--a carefully staged press conference to carry the message to the American public. (36)

#### In the Aftermath of the Surgeon General's Report, 1964-65

With the release of the Advisory Committee's report on January 11, 1964, the purely scientific phase of the cigarette controversy had largely run its course. Almost immediately, the controversy shifted to the political realm--a clash between public health considerations on the one hand and private economic interests on the other. The stakes were evident from the outset. The mere issuance of the Surgeon General's report, coupled with the attendant publicity, produced a short-run, one-month decline in cigarette sales of more than 15 percent. (37) But more significant than this temporary impact was the fact that the report's release



signalled the nation's embarkation along a twisting pathway in search of an appropriate cigarette policy. It is now clear that at several points along that pathway--stretching from 1964 to 1971--advocates for the public's health stumbled across the elements of a truly effective program in cancer control education, only to have the Congress intervene to block the emerging policy and then redirect it along predictably unproductive lines.

In the winter and spring of 1964, there was no requirement that the Congress act in response to the Surgeon General's report. In fact, it is likely that no action at all would have been forthcoming had it not been for the maverick-like conduct of the Federal Trade Commission, particularly its Chairman, Paul Rand Dixon, and commission member, Philip Elman. Citing the Surgeon General's report, and then citing its authority to regulate commerce so as to eliminate unfair and deceptive trade practices, in a classic document of administrative law, the FTC proposed a trade regulation rule which would have required in every cigarette advertisement (radio, television, billboards, and print media) and on every pack, box, and carton of cigarettes, the prominent inclusion of one of the following warnings:

(1) CAUTION--CIGARETTE SMOKING IS A HEALTH HAZARD: The Surgeon General's Advisory Committee on Smoking and Health has found that "cigarette smoking contributes substantially to mortality from certain specific diseases and to the overall death rate;" or

(2) CAUTION: Cigarette smoking is dangerous to health. It may cause death from cancer and other diseases. (38)

The fact that the regulation would have required the labeling of one of these warning statements on every pack, box, and carton of cigarettes was not nearly as significant as the requirement that the statement accompany any advertising, including broadcast advertising. A disclosure statement



of the kind proposed by the FTC threatened to destroy the appeal of radio and television advertising, an appeal of such enormous dimensions that the industry was pumping nearly \$200 million per year--four-fifths of its advertising expenditures--into these media.

Faced with the impending FTC action, the tobacco lobby, whose principal lobbyist was former Congressman Earle C. Clements (D-Kentucky), turned to the Congress for help. (39) In substantial measure, the industry received all the help it needed with the Federal Cigarette Labeling and Advertising Act of 1965. (40) In this act, Congress blocked the FTC's proposed regulations and required instead that as of January 1, 1966, all cigarette packages, boxes, and cartons sold in the U.S. must bear the statement: "Caution: Cigarette Smoking May be Hazardous to your Health." Beyond this inconspicuous side-panel requirement, the Congress refused to require that the mildly worded warning statement accompany radio and television advertising--the key to the promotion of cigarette sales. In fact, the labeling act expressly banned the FTC, and any state or local agencies, from taking any action in this regard for a period of four years. Senator Frank Moss (D-Utah) later lamented that the 1965 legislation effectively suspended the entire apparatus of federal and state regulatory authority in exchange for nine innocuous words on the side-panel of cigarette packages. Representative John Moss (D-Calif.) voiced his opposition in these terms:

This legislation puts the Federal Government in the position of saying that cigarette smoking constitutes a serious health hazard, but that traditional guardians of public health, the state and local authorities, cannot act to protect their citizens if they believe a warning statement in cigarette advertising would do so. (41)

The warning requirement, he said,

does little to act as a remedy to curb the cigarette health hazard... .A more realistic and responsible approach. . .would be to warn the non-smoking consumer of the health hazard before the product is purchased--rather than remind the individual who already smokes and after he has the product in his possession, that it may be harmful to his health. . . .We must first concern ourselves with public health and welfare, not legislate to the whims of a special interest. (42)

When the labeling requirements went into effect on January 1, 1966, there was no significant impact on cigarette sales; per capita consumption increased slightly in 1966. (43)

By way of separate legislation, the Congress took other action in the cigarette field in 1965. As a means of maintaining the staff which had served the Surgeon General's Advisory Committee, the Congress appropriated \$2 million to the Public Health Service to establish a National Clearinghouse on Smoking and Health. (44) Lodged in the Cancer Control Program in the Division of Chronic Diseases, the Clearinghouse undertook responsibility for gathering and disseminating information on smoking and health including, later on, the preparation and promotion of anti-cigarette media messages. Under the direction of Daniel Horn, who had contributed to the pioneering scientific work on tobaccogenic cancer, the Clearinghouse, tiny as it was, nevertheless represented the only programmatic evidence of a national effort to discourage cigarette smoking.

#### The Banzhaf Decision and Congressional Re-entry, 1967-71

In mid-1967, a year and a half after the labeling act took effect, a young attorney named John Banzhaf III filed a Fairness Doctrine complaint with the Federal Communications Commission. In his complaint, he called upon the FCC to make a finding that cigarette commercials per se con-

stituted statements depicting one side of a controversial issue of public importance and that, accordingly, the Federal Communications Act required the FCC to order stations to provide "equal" time for the presentation of the "other side" of this public controversy. In a landmark decision, the FCC agreed with much of Banzhaf's argument and required broadcasters to accord a "substantial" amount of air time--although not "equal" time--to the "other side" of the cigarette controversy. (45)

With this decision, the nation was launched on a three-and-a-half-year experiment in public health education by way of anti-cigarette commercials. Affirmed by the courts in 1968, (46) the FCC action was interpreted to mean that radio and television stations had to provide roughly one free anti-cigarette message for every five pro-cigarette messages. (47) Translated into aggregate terms, this meant that by 1969 and 1970, approximately \$40 million per year in broadcast time--free of charge--was accorded to the American Cancer Society, the Tuberculosis Association, and other non-profit organizations in order to present hard-hitting anti-cigarette messages. It was a unique era in broadcast advertising, giving rise to a host of creative anti-cigarette messages. For example, there were the messages depicting a pleasant scene: people having fun, enjoying life. Then one of the people would light up a cigarette and the voice-over caption would follow: "This is life. . . . This cuts it short." Another spot message was a parody of the Marlboro man. A tough-looking, gun-toting cowboy pushed his way into a saloon, inhaling a smoky cigarette. Then he began to cough uncontrollably, and was pushed aside by a clean-cut, non-smoking cowboy. Then the word "cancer" zoomed up on the television screen and the voice-over announcer



said, "Cigarettes--they're killers."

Perhaps the most forceful of the anti-cigarette messages on television was the one in which William Talman, the actor who played Hamilton Burger on the Perry Mason series, introduced his family and then revealed that he had lung cancer. He then urged smokers to quit and non-smokers not to start. By the time this particular anti-cigarette message was on the air, William Talman was dead from lung cancer.

While the FCC facilitated the era of anti-cigarette messages, it is interesting to note that this novel venture in public health education had its beginnings in the voluntary sector, not the public sector. Indeed, both in its origin and in its content, the anti-cigarette campaign was almost exclusively a product of the voluntary sector. And even within that sector, some traditional voluntary health agencies, most notably the American Cancer Society, were unwilling to back the initial Banzhaf complaint. (48)

During the years 1967-1970, the Banzhaf decision had a major impact on per capita cigarette consumption. After years of virtually uninterrupted growth in per capita consumption, there was a slight fall-off in 1967--4280 cigarettes for every U.S. resident 18 years of age and older as compared with 4287 in 1966. (49) In 1968, per capita consumption fell again--to 4186 units. (50) In 1969, when monitoring and public pressure was assuring widespread compliance with the Banzhaf decision, anti-cigarette messages were in full swing; and per capita consumption suffered its most severe drop-off, down to 3993 units. (51) In 1970, a further decline was registered, down to 3985 cigarettes. (52) (See Figure 1,)

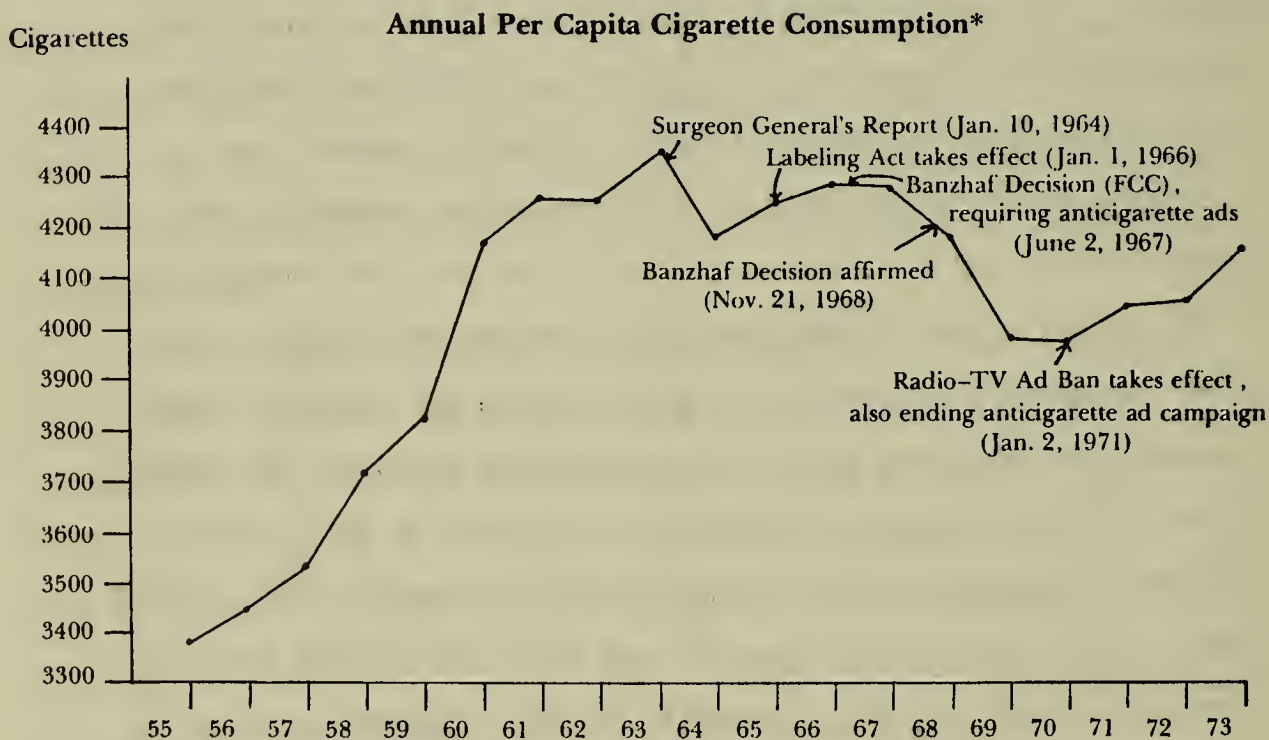


During 1969, Congress re-entered the picture. Its 1965 legislation prohibiting FTC regulation of cigarette advertising was scheduled to expire on June 30, 1969. Seizing this opportunity, Congress intervened in the cigarette controversy for the second time. It enacted the Public Health Cigarette Smoking Act which included two principal provisions. First, in a minor concession to the flood of scientific evidence concerning the deleterious effects of cigarette smoking, the Congress changed the cigarette side-panel label to read: "Warning: The Surgeon General Has Determined That Cigarette Smoking Is Hazardous To Your Health." The second provision, which appeared to be a victory for public health advocates, was to ban radio and television cigarette advertising effective January 2, 1971. Privately, however, the cigarette manufacturers favored a radio-television advertising ban. (53) They believed--as it turns out correctly--that such a ban would serve to undo the anti-cigarette campaign tied to the Banzhaf decision. With the banning of pro-cigarette commercials, radio and television broadcasters were no longer under a legal obligation to present the "other side" of the controversy. Accordingly, on January 2, 1971, the anti-cigarette messages virtually vanished from the airwaves. The country's three-and-a-half-year experiment in mass media anti-smoking education dried up almost overnight. Meanwhile, in 1971, cigarette promoters managed to shift \$150 million of their more than \$200 million per year in radio and television expenditures into other outlets, principally newspapers, magazines, and billboards. (54)

The effect of all this upon per capita consumption was dramatic. After an historic four-year decline in consumption, an upward trend returned in 1971. In that year, per capita consumption rose to 4037 from

the previous year's 3985. (55) In 1972, the figure went to 4043; (56) and in 1973 leaped sharply to 4147. (57) By 1973, per capita cigarette consumption was approaching the 1963 peak figure of 4286. (58)  
(See Figure 1.)

FIGURE 1



Source: U.S. Department of Agriculture

\*For the year 1960 and subsequent years, per capita consumption figures maintained by the government were calculated by dividing the total number of cigarettes consumed by the number of Americans eighteen years or older. In earlier years, the calculation had been based on the number of Americans fifteen years or older.

The Federal Trade Commission was so alarmed at the turnaround in cigarette sales that it recommended to the Congress in 1971--and repeatedly in the years since--that funds be allocated to HEW to enter the marketplace and purchase radio and television time for anti-cigarette messages, in order to effectively re-establish the public health education program which flourished from 1967-1970. (59)

Paralleling the legislative reversals, the National Clearinghouse on Smoking and Health also suffered a series of setbacks in the late 1960s. In 1967, the Clearinghouse went the way of its parent unit, the Cancer Control Program, and was shifted to the Regional Medical Programs Service, an organizational switch which made little sense in terms of the Clearinghouse's work but was indicative of its posture as a programmatic foster child, seemingly unwanted because of the powerful congressional opposition which was part-and-parcel of its operations. In 1971, the Clearinghouse was moved again, this time to the Center for Disease Control; meanwhile, its budgeted appropriations were declining. In November of 1974, the Clearinghouse was physically re-located from the Washington, D.C., area to Atlanta, Georgia. At the same time, its line item budget, less than \$1.5 million in fiscal year 1974, was removed. With the loss of funding and with the move to Atlanta, the Clearinghouse was effectively reduced to a programmatic nonentity. Dr. Horn, the Clearinghouse's Director since its inception, resigned.

In evaluating the Congress' role as handmaiden to the tobacco interests, Dr. Ernst Wynder observed:

The fundamental law of the politician is first to be elected. If you don't get elected, you can't do anything. If you took a position that you thought smoking was the worst thing, and you came from a tobacco-growing state, you would never get elected. So that's how you have the tobacco bloc.



And the way Congress works, because of seniority, tobacco states supply the committee chairmen. They say, 'Okay, now you work for me in this area and I'll work for you in that area.' ...That's why so many of these blocs are successful perpetuating their particular line of propaganda. (60)

Statistical underpinning for Wynder's political observation rests with the fact that an estimated 600,000 farm families, heavily concentrated in the Southeast, derive part or all of their livelihood from tobacco sales. (61)

To further illustrate his point about the dynamics of special interest politics, Wynder noted his own experience in challenging the meat and dairy interests on the question of cholesterol and, in the case of fatty meats, on the question of diet-related colon and breast cancers:

The meat industry of course is very powerful, and so is the dairy industry. All together, they are infinitely more powerful than the tobacco industry. It is interesting, without mentioning names, I went to see one Congressman once--from one of the tobacco states. He said, 'You must understand that I have to do what I do because otherwise I can't be elected. But nutrition, I'll help you all the way.' Some time later I saw a Senator from one of the dairy states who said, 'I am certainly anxious to help you in the tobacco area. But the dairy area, leave it alone.' (62)

### Reflections on the History of Tobaccogenic Cancer

. In reviewing the steps leading to the current near-unanimity regarding the carcinogenicity of tobacco, there are no discrete points that can properly be labeled dramatic breakthroughs. Instead, the history reveals a process of evidentiary accumulation: first, the relatively small-scale clinical studies; then a series of retrospective epidemiological studies; and, finally, a number of large-scale prospective studies.



. The 1964 report of the Surgeon General's Advisory Committee on Smoking and Health had the effect of rendering a scientific judgment on the significance of the evidence at hand. Largely because of Surgeon General Terry's adroit political management, the Advisory Committee's conclusion on cigarette-lung cancer causation had maximum scientific impact.

. The period 1964-1971 placed the cigarette controversy in an intensely political arena. Congressional policymaking was dominated by special interest lobbying, with the tobacco lobby able to exert enormous influence through the traditional avenue of Southern committee chairmen. The result was a feeble congressional response in 1965 to the Surgeon General's 1964 call for prompt "remedial action" to meet the serious health hazard posed by cigarettes.

. After the almost accidental discovery of a successful anti-cigarette policy--through the Federal Communication Commission's 1967-1970 application of the Fairness Doctrine to radio-TV cigarette advertising--the Congress was once again able to reassert its primacy in the cigarette policy field, to the ultimate detriment of the public's health. There was no presidential leadership forthcoming to promote a more health-oriented legislative response in these critical years. Nor, for that matter, was there leadership forthcoming from the National Cancer Institute where, apparently, considerations of long-range congressional funding of research took precedence over the need to develop a more effective cigarette-cancer control policy.

Chronology of Significant Events in the History  
of Tobaccogenic Cancer

- Mid-1930s Dr. Alton Ochsner suspected cigarette smoking as a causative factor in an observed clinical "epidemic" of lung cancer.
- 1939 Müller published one of a number of European studies indicating a statistical association between cigarette smoking and lung cancer.
- 1941 Drs. Alton Ochsner and Michael DeBakey published the first American study, based on clinical observations from autopsies, which stressed the cigarette-lung cancer connection.
- 1950 Drs. Ernest Wynder and Evarts Graham published the results of their retrospective epidemiological study, concluding that cigarette smoking "seems to be an important factor in the inducement of bronchiogenic carcinoma."
- Early 1950s A number of retrospective studies followed the Wynder-Graham effort, with investigators observing strikingly similar findings.
- 1953 Graham and Wynder produced skin cancer in animals by applying the tar from cigarette smoke.
- Late 1950s The results from a series of prospective epidemiological studies are published, (the Doll and Hill study of British doctors--1956, the Hammond-Horn American Cancer Society study--1958, the Dorn study of U.S. War Veterans--1959). The strong relationship between prolonged cigarette smoking and lung cancer was found in each of the studies.
- 1959 After more than a year of internal review, Surgeon General Leroy Burney published a statement in the Journal of the American Medical Association implicating smoking as the principal etiological factor in the increasing incidence of lung cancer.
- 1962 The Royal College of Physicians in London published their report concluding that cigarette smoking was causally related to lung cancer.
- 1964 Surgeon General Luther Terry released the report of his Advisory Committee on Smoking and Health, concluding that cigarette smoking was causally related to lung cancer in men.
- 1965 The Congress blocked pending Federal Trade Commission regulations controlling cigarette advertising, adopting instead a mild cautionary statement to appear on cigarette package side-panels.

- 1967      The era of anti-cigarette messages in radio-TV broadcasting began with the FCC's Fairness Doctrine decision. Per capita cigarette consumption began to decline.
- 1971      The Public Health Cigarette Smoking Act took effect, banning radio-TV pro-cigarette advertising and simultaneously ending the anti-cigarette media campaign. Per capita consumption began to rise.

Notes: Chapter 3

- (1) Ochsner, A.: My first recognition of the relationship of smoking and lung cancer. Prev. Med. 2:611-614.
- (2) Cancer Facts and Figures. New York, American Cancer Society, 1976.
- (3) See note (2) at 5.
- (4) See note (1) at 611.
- (5) Muller, F.H.: Tabakmissbrauch und Lungencarcinom. Z Krebsforsch 49:57-85, 1939.
- (6) Ochsner, A., DeBakey, M.: Carcinoma of the lung. Arch. Surg. 42:209-258, 1941.
- (7) See note (6) at 210.
- (8) See note (6).
- (9) Shimkin, M.B.: Adventures in cancer epidemiology. Cancer Res. 34:1525-1535, 1971, at 1527.
- (10) See note (1) at 613.
- (11) See note (1) at 613.
- (12) Wynder, E.L., Graham, E.A.: Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. J.A.M.A. 143: 329-336, 1950.
- (13) See note (12) at 336.
- (14) Wynder, E.L., Graham, E.A., Croniger, H.B.: The experimental production of carcinoma with cigarette tars. Cancer Res. 13:855-864, 1953.
- (15) See note (1) at 614.
- (16) Interview with Dr. Ernst Wynder, President of the American Health Foundation, by Larry Agran of HCCP, April, 1976, New York City.
- (17) Interview with Dr. Lester Breslow, Dean of the UCLA School Of Public Health, by Larry Agran of HCCP, November 25, 1975, Los Angeles, Ca.
- (18) Breslow, L., Hoaglin, L., Rasmussen, G., et al: Occupations and cigarette smoking as factors in lung cancer. Am. J. Pub. Health 44:171-181, 1954.



- (19) See note (17).
- (20) Hammond, E.C., Horn, D.: Smoking and death rates--report on forty-four months of follow-up of 187,783 men. J.A.M.A. 166: 1159-1172 (Part I, Total Mortality), 1958: and J.A.M.A. 166: 1294-1308 (Part II, Death Rates by Cause), 1958.
- (21) See note (20).
- (22) Doll, R., Hill, A.B.: Lung cancer and other causes of death in relation to smoking. Brit. Med. J. 1071-1081, November 10, 1956.
- (23) Dorn, H.F.: Tobacco consumption and mortality from cancer and other diseases. U.S. Pub. Health Rept. 74:581-593, July, 1959.
- (24) See note (20).
- (25) Burney, L.: Smoking and lung cancer: a statement of the Public Health Service. J.A.M.A. 171:1829-1837, November 28, 1959.
- (26) See note (25).
- (27) Smoking and Health. Report of the Royal College of Physicians. London, 1962.
- (28) Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Dept. of HEW, 1964.
- (29) See note (28) at 182.
- (30) See note (28) at 196.
- (31) Trade Regulation Rule for the Prevention of Unfair or Deceptive Advertising and Labeling of Cigarettes in Relation to the Health Hazards of Smoking, and Accompanying Statement of Basis and Purpose of Rule. Federal Trade Commission, June 22, 1964, at 8-24.
- (32) See note (31).
- (33) See note (31).
- (34) Interview with Dr. Luther L. Terry, former Surgeon General of the U.S. Public Health Service, by Myrna Morganstern of HCCP, April, 1976, New York City.
- (35) See note (34).
- (36) See note (34).

- (37) Statistical Supplement to Federal Trade Commission Report to Congress Pursuant to the Public Health Cigarette Smoking Act, 1974, at 4.
- (38) See note (31) at Appendix D.
- (39) Health Warning Required on Cigarette Packs. Congressional Quarterly Almanac 344-351, 1965.
- (40) 15 U.S.C. Sections 1331-1339 (Supp. 1966).
- (41) See note (39).
- (42) See note (39).
- (43) Annual Report on Tobacco Statistics: 1973. U.S. Dept. of Agriculture, April, 1974, at 33.
- (44) See note (39).
- (45) Applicability of the Fairness Doctrine to Cigarette Advertising. 9 F.C.C. 2d 921, 1967.
- (46) Banzhaf v. FCC, 405 F.2d 1082, 1968.
- (47) National Broadcasting Co., Inc., 16 F.C.C. 2d 947, 1969.
- (48) Whiteside, T.: Selling Death: Cigarette Advertising and Public Health. New York, Liveright, 1971.
- (49) See note (43).
- (50) See note (43).
- (51) See note (43).
- (52) See note (43).
- (53) House and Senate Disagree on Cigarette Ad Bill. Congressional Quarterly Almanac 883-890, 1969.
- (54) Statistical Supplement to Federal Trade Commission Report to Congress Pursuant to the Public Health Cigarette Smoking Act, (Table 7), 1973.
- (55) See note (43).
- (56) Annual Report on Tobacco Statistics: 1975. U.S. Dept. of Agriculture, April, 1976, at 28.
- (57) See note (56).

- (58) See note (56).
- (59) Federal Trade Commission Report to Congress Pursuant to the Public Health Cigarette Smoking Act, December 31, 1974, at 10-11.
- (60) See note (16).
- (61) Tobacco in the National Economy. U.S. Dept. of Agriculture, 1975. (mimeo)
- (62) See note (16).





## CHAPTER 4

### DETECTION OF UTERINE CERVIX CANCER

#### Introduction

In September 1926, the eminent pathologist, Dr. James Ewing, speaking at an International Symposium held under the auspices of the American Society for the Control of Cancer, described the generally grim outlook for the early diagnosis and control of cervical cancer.

Since early cervical cancer gives no specific symptoms, one cannot rely upon early diagnosis....There are two resources available, the insistent repair of cervical lesions after childbirth, and periodic examinations, during and after the child-bearing period. Since cervical cancer develops abruptly, and advances to a serious condition in many cases within a few weeks or months, these examinations must be made at least every six months, in suspicious cases, and once a year in others....The practical difficulties of instituting such measures for the general population are very great. (1)

In 1969, Dr. Charles Cameron, former Medical Director for the American Cancer Society and himself a principal figure in the advancement of cervical cytology, delivered the keynote address at the World Conference on Cancer of the Uterus, in New Orleans. (2) Contrary to Ewing's depressing assessment of 43 years earlier, Cameron could speak in the most optimistic terms about the prospects for the control of cervical and uterine cancer:

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[A] technique of diagnosis is now at hand which can disclose [cancer of the cervix] while it is curable;... effective means of treating it, in terms of skill and material, are now generally available and are steadily increasing in many countries of the world. This happy jointure of circumstance suggests that uterine [cervical] cancer's time has come. (3)

Dr. Cameron's characterization was not a matter of unsubstantiated optimism. It was a reflection of the reality that in the 43 years since Ewing's 1926 statement, the control of carcinoma of the cervix had gradually become an achievable goal. Table 1 indicates that uterine cancer mortality (age-adjusted and including both cervix uteri and corpus uteri) has fallen from over 27 deaths per 100,000 U.S. white females in 1935 to about 8 per 100,000 in 1973.

Table 1: Mortality Rates from Uterine Cancer\*

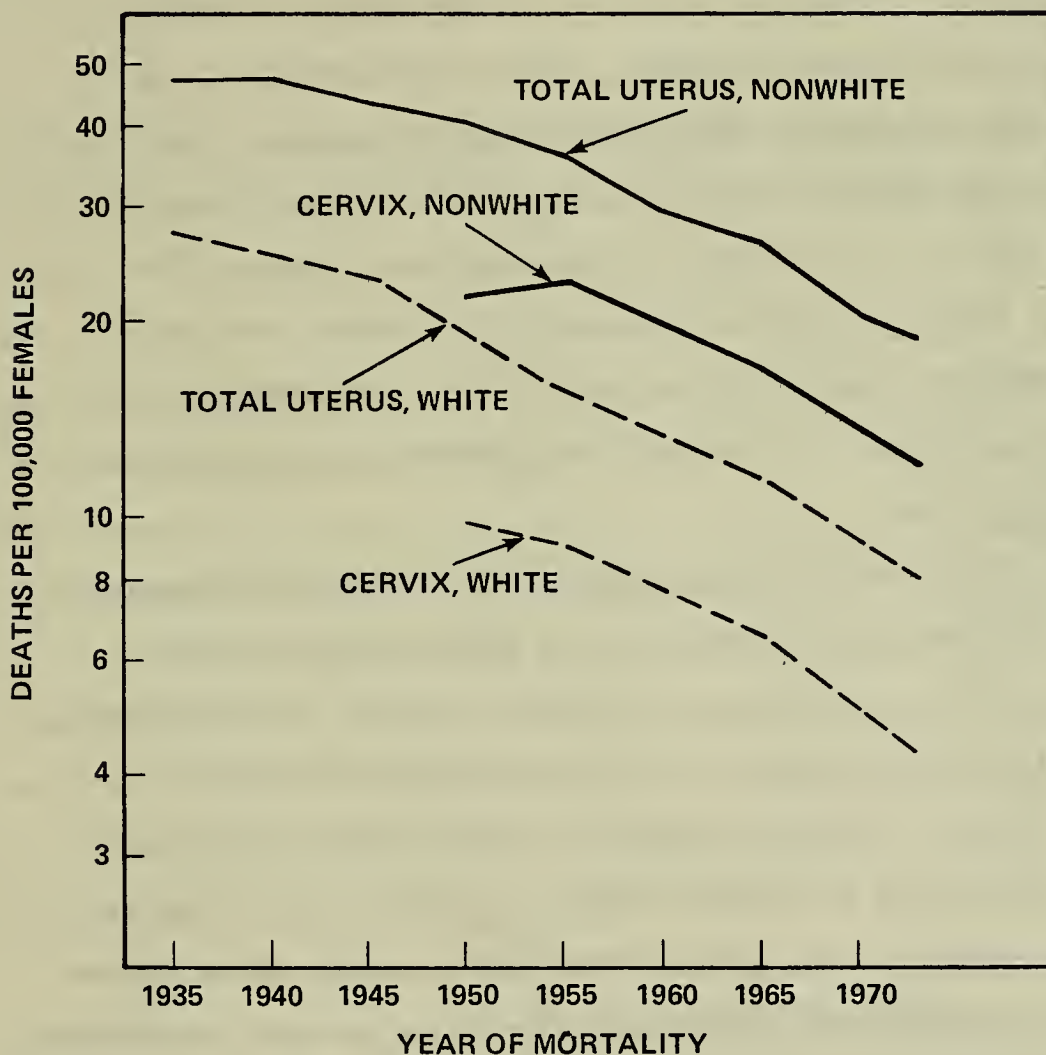
<u>Year</u>	<u>Uterus (total)</u>		<u>Cervix</u>	
	<u>White</u>	<u>Nonwhite</u>	<u>White</u>	<u>Nonwhite</u>
1935	27.4	47.2		
1940	25.5	47.6		
1945	23.3	43.6		
1950	19.0	40.6	9.8	21.8
1955	15.8	36.1	9.1	23.0
1959-61	13.3	29.4	7.8	19.5
1964-66	11.7	26.5	6.6	16.8
1969-71	9.1	20.5	5.1	13.5
1973	8.1	18.9	4.3	12.0

\*Deaths per 100,000 females - age-adjusted.

Source: Unpublished NCI data.

Rates for nonwhite women declined from 47 to 19 per 100,000 females. Accurate data are available for cervical cancer alone since 1950 and, as can be seen from Table 1, the trend is similar. Figure 1 offers a graphic illustration of this fall in mortality.

Figure 1



From 1950 to 1975, approximately 200,000 American women died because of cervix cancer. If the far more favorable 1975 rates had applied during this entire period, the total loss would have been almost 70,000 fewer deaths.

What has been the reason for the decline in cervical cancer mortality? While a conclusive explanation for this fortunate experience has not been possible, several factors appear to have contributed to the decline. Advances in treatment have led to an improvement in survival rates and a decline in the death rate. But these achievements do not explain the drop in mortality during the last quarter century. End results data show that improvements in cure rates very likely played a significant role up to the 1950s, but since that time, trends in five-year survival rates for patients with cancer of the cervix uteri have shown no significant change. (4) The reason for the continuing decline in mortality is apparently attributable to a separate factor--prevention of the invasive disease.

What is being accomplished, apparently, is an avoidance of invasive disease through detection and treatment of a precursor state, namely carcinoma in-situ, an early stage in the disease process. Preventing the occurrence of invasive disease is not to be interpreted as prevention of the disease itself. There are currently no specific means of avoiding or preventing the onset of the disease process. But that is not to say that nothing has occurred that may have influenced the incidence of the disease. Epidemiological studies have associated a high rate of cervical cancer with low socio-economic groups; with women who marry early; and with women experiencing early pregnancy and a high number of pregnancies. The apparent racial difference in risk has been considered a socioeconomic



phenomenon with early sexual activity playing a major part. (5) Thus it is possible that the measurable economic gains and improved general health conditions of this segment of the population would tend to decrease the incidence of cervical cancer. Other factors, such as the increase in the number of hysterectomies performed in the United States since the end of World War II, have also decreased the population at risk for uterine cancer, although not nearly to an extent sufficient to explain the substantial drop in mortality. (6)

The factor most frequently accepted as being of overriding significance in reducing the incidence and mortality of carcinoma of the cervix has been cytologic screening--the use of the Papanicolaou test as a means of diagnosing cancer before it has progressed to an invasive stage. Yet, even today, because of a lack of definitive epidemiological evidence, there is no firm consensus as to the impact of cytologic screening. Why was the effectiveness of cervical cytology as a screening procedure never adequately tested? If its effectiveness is as great as some have claimed, why has cytologic screening been in widespread use only in the past few years? To address these and other questions relating to early diagnosis of cervical cancer, it is necessary to review events both before and after the development of cytology as a method for early cancer detection.

#### Early Diagnosis by Direct Visualization

During the first part of the century, the general outlook for cervical cancer was poor and early diagnosis did not play any significant role. It was in this climate of pessimism that Dr. Ewing summarized the control prospects with his observation that "the practical difficulties of instituting [periodic examinations] for the general population are very

great." (7) However, almost coincidental with Ewing's 1926 statement, there were several significant clinical developments taking place which helped further the early diagnosis of cervical cancer. Among these were the development of colposcopy and the Schiller iodine test. These advances were possible only because of preceding studies on the pathologic features of early cervical cancer, from an original description in 1886 of epithelial change in the cervix portio (8) to studies more than 22 years later that established the significance of these changes by identifying them as the earliest stage of carcinoma of the cervix. (9,10,11,12) Dr. Leopold Koss, Professor and Chairman of the Department of Pathology at the Albert Einstein College of Medicine, Montefiore Campus, recently reflected on these early advances in pathology.

[A] key contribution was by a man named Schauenstein, who in 1907 published a key paper as a part of his doctoral thesis (13)...on the development of carcinoma of the uterine cervix. In this paper he pointed out that prior to invasion...there was an identifiable state of cervix cancer which was confined to the epithelium of origin. This paper, for the first time, introduced the idea that the carcinoma, that is, the cancer of the epithelium, originated from abnormal epithelium. This was the first time that this matter had been so clearly stated. It was of such interest that subsequently a number of people...worked on this topic. One of them was a gynecologist from Mount Sinai in New York. His name was Rubin. Rubin wrote a paper in 1910 (14) in which he confirmed Schauenstein's observations on early stages of carcinoma of the uterine cervix....There was also a major book published...by Schottlaender and Kermauer (15)...in which another important point was made and that was the separation of cancer of the cervix from cancer of the endometrium. Schottlaender and Kermauer separated the two and spoke of carcinoma in-situ....The German word is oberflachen carcinom, meaning surface cancer. (16)

In 1924, Hinselmann invented the colposcope as a means of providing magnification of the cervix to aid in diagnosis. (17) Enlargement of the field of view was obtained by the use of a magnifying glass, and magnification up to 40 times was attempted. But difficulties in focusing and

a relatively small field size limited the colposcope's utility. In 1950, Antoine and Grumberger presented the colpomicroscope rather than a magnifying glass. (18) As a result, at these higher magnifications it was possible also to visualize actual cell structures.

Colposcopy has had widespread use in Europe and South America, but there has been little general interest in the United States. For the most part, gynecologists in the United States were unfamiliar with the colposcope and until recently have made little effort to learn the method. Possible reasons for this delay have been suggested:

First has been language difficulties and the lack of scientific papers in English on the subject. Second has been the necessity of learning many new and unfamiliar terms. Third, the colposcopist requires a good knowledge of the histopathology of dysplasias which, until recently, have received little attention in standard gynecology and pathology texts or in the English medical literature. Fourth, the appearance on the scene of the diagnostic method of exfoliative cytology almost certainly has retarded the development of colposcopy, certainly in the U.S. Many presumed that the sole purpose of colposcopy was to detect early carcinomas of the cervix, and, therefore, if cytology provided all the answers to this problem colposcopy was unnecessary. With experience, the many deficiencies of exfoliative cytology have now become apparent and the complementary value of the method of colposcopy is obvious to those who have used it critically. Finally, there have been the published comments of some eminent gynecologists and pathologists throwing much doubt on the value of this instrument. (19)

American gynecologists were always in a hurry and you cannot do colposcopy in such a tremendous hurry. You have to have your patient rest comfortably for a period of anywhere from three to fifteen minutes, depending on what is found, and the American gynecologists were quite convinced that no American female would be willing to sit in a gynecologic posture for such a lengthy period of time. I rather suspect that they didn't think they had the time to devote. (20)

The main use of the colposcope today is to aid in the diagnosis and evaluation of patients with abnormal cytology and to help direct the biopsy and possibly avoid unnecessary biopsies. Colposcopy is too time consuming



to use as a general screening technique. It is a relatively specialized procedure that requires constant practice to achieve and retain proficiency. It is best suited for institutions in which a large enough number of patients with abnormal cytology are seen to utilize a trained colposcopist effectively. An adequate patient workup can be performed without colposcopy if the Schiller test is used and the examining clinician is willing to biopsy any grossly evident abnormality detected by the test. (21)

The Schiller test was developed by a pathologist, Walter Schiller, who noted that cancer cells failed to contain as much glycogen (a complex sugar) as normal cells. Based on this observation, in 1928 he developed the now widely used Schiller iodine test to help locate suspicious areas of the cervix more easily and quickly. (22) By painting the cervix with Lugol's iodine solution, diseased areas are stained and readily differentiated from normal epithelium. The application of Lugol's solution is used today as an adjunct in the diagnosis of carcinoma in-situ and to help in delineating biopsy sites after a suspicious smear report. It too must be administered by an examiner experienced with the test.

#### Development of Cervical Cytology

Undoubtedly the major development appropriate for use in detection of cervical cancer in the general population has been cytologic screening. Exfoliative cytology of the female genital tract reaches back to 1847 when Pouchet published a report dealing with normal cells obtained from vaginal secretions, (23) but it was not until the early part of this century that cytological diagnosis of cancer received more than occasional attention. (24)



Because the use of cytology in the detection of uterine cancer received its main impetus in the United States from the pioneering work of Dr. George N. Papanicolaou, the Greek-born and educated Dr. Papanicolaou is generally identified as its developer, and his name is frequently associated with its use--the "Pap" smear. What is not widely known is that another individual, Dr. Aurel A. Babes, obtained similar results at about the same time and presumably independent of Dr. Papanicolaou. Dr. Babes, a pathologist from Bucharest, Rumania, first reported his method to the Society of Gynecology of Bucharest in January 1927. (25) Then, in 1928, in a major paper in the French medical journal, La Presse Medicale, Babes described his cervical smear method of diagnosis of cervical cancer. (26) Babes stated that he developed the smear method to identify atypia in cervical cancer lesions because atypia seemed to be a characteristic of early development of cancer. His paper raised two main points:

- . that the appearance of invasive cancer of the uterine cervix is preceded by abnormalities of epithelial cells; and
- . that smear material could be obtained by rubbing suspicious lesions with a platinum loop.

Dr. Babes persuaded his colleague, Dr. C. Daniel, who worked in the Gynecologic Clinic of Bucharest, to use the smear method in the examination of 20 cases of cancer of the uterine cervix. Using this case material, Babes was able to describe the histopathologic features of smears in cancer. Dr. Babes concluded his 1928 paper by stating that while they were able to present initial evidence to support the usefulness of the smear method in cervical cancer diagnosis, future investigations were necessary

to determine its precise role in diagnosis of cervix cancer. (27,28)

The work of Dr. Babes influenced Dr. Odorico Viana, Director of the Royal Obstetrical College of Verona (Italy); to study also the role of smears in the diagnosis of uterine cancer. (29) In reporting his results on 12 cases in 1928, Dr. Viana did not feel that he could draw conclusions regarding the method. He pointed out shortcomings of the smear technique and urged further investigations in the hope that the method might prove useful for internal organs that are not accessible for biopsy. (30)

Apparently quite separately from Babes' and Viana's work, in January, 1928, Dr. Papanicolaou presented his first cancer-oriented paper on the subject of abnormal features of certain cells found in smears of vaginal secretions of women with uterine cancer. (31) These results were a direct consequence of his interest and work in the physiology of the reproductive organs and particularly problems of ovogenesis. (32,33) In this early work, Dr. Papanicolaou determined the time of ovulation in guinea pigs by studying changes in the consistency and makeup of vaginal fluid during ovarian and uterine cycles. This work led to results on the use of the vaginal smear method as a means of studying certain problems related to the morphology and physiology of reproductive organs in women. To be able to determine what was normal and what was abnormal, Dr. Papanicolaou studied changes in smears associated with important pathologic conditions, including malignant tumors of the ovaries, uterus, cervix and vagina. The short paper he delivered in 1928, entitled "New Cancer Diagnosis," reported preliminary observations on the smear changes which accompanied well expressed cases of malignant tumors of the genital tract. (34) Dr. Koss, who later became a friend and colleague of Dr. Papanicolaou, had the following thoughts:

He came across some cells in these smears...which he couldn't interpret. They were odd looking cells, so to the best of my knowledge what he did was to consult the then leading cancer pathologist in the world, Dr. Ewing. Ewing was then professor of pathology at Cornell and also the pathologist at the Memorial Hospital for Cancer. Ewing apparently told him that these might be cancer cells. (35)

The early work of Babes, Viana, and Papanicolaou on the utilization of cervical cytology for the detection of cervical cancer received little recognition or encouragement by the medical profession. It was not until after World War II--nearly two decades after the early breakthroughs in cervical cytology--that the first large-scale efforts in cytologic screening began, and these were in the United States. Why did it take so many years to seize upon the potential of cervical cytology in controlling cervical cancer?

The early reference in 1928 by Papanicolaou to the potential usefulness of the cytologic smear method in the detection of cancer of the uterus was published in the proceedings of the Third Race Betterment Conference held at the Battle Creek Sanitorium, Battle Creek, Michigan. (36) The conference was not a medically oriented meeting, but rather was directed toward a wide variety of societal problems. Why Dr. Papanicolaou chose to present his findings at this conference is not clear. Whatever the reason, his paper apparently failed to attract any significant attention among medical professionals. But the paper did receive the attention of the press, and a newspaper article published by the New York World announced Papanicolaou's work as the discovery of a new method in diagnosing certain kinds of human cancers. (37) Dr. Papanicolaou later lamented that his paper was "almost totally ignored chiefly because of its brevity and its insufficient documentation." (38) According to his later writings, Dr. Papanicolaou recognized that he had failed to interest his



colleagues in the practicality of the procedure.

The prevailing opinion, as expressed by one of the outstanding pathologists of that time, was that since the uterine cervix was accessible to diagnostic exploration by biopsy, which is a relatively simple procedure, the use of the cytologic examination of vaginal smears appeared to be superfluous. (39)

At that time gynecologists were no more attentive than pathologists to his findings.

[G]ynecologists of that time were largely pre-occupied with problems related to the cyclic manifestations of morphologic changes in the vaginal and cervical epithelium, and their correlation with the ovarian and uterine cycles. (40)

Even though in his 1928 report he made an optimistic prediction that his work would be carried further and that some diagnostic method would be developed in the future, Papanicolaou did not reorient his own research activities toward greater emphasis on cancer. Due to the lack of enthusiasm among his colleagues for his "cancer discovery," he continued to focus his cytologic research on endocrine problems. (41)

Five years later, in a 1933 paper describing the collection, staining and classification of normal smears and their application in analysis of the human female sex cycle, Dr. Papanicolaou briefly referred back to his 1928 report and stated that he would give this research area more attention in a future paper:

In the last few years attention has been given to the characteristic smear changes which seem to accompany cases of malignant tumors of the genital tract. A preliminary report on these observations was given at the 'Third Race Betterment Conference' (1928). Several types of abnormal cells with enlarged, deformed or hyperchromatic nuclei are present in such smears....A more detailed discussion of this phase of the study will be given in a subsequent publication. (42)



Dr. Bernard Naylor, in writing a history of exfoliative cancer cytology, referred to Papanicolaou's 1928 report and confirmed that it was more than just a lack of interest by the medical profession that kept Dr. Papanicolaou from continuing his cancer studies:

This early study was received with much skepticism, not that the morphologic soundness of the method was questioned, but its practical value and dependability as a diagnostic procedure was looked upon with mistrust. (43)

Because of this unfavorable reception among those who were aware of his work, Dr. Papanicolaou did not return to studying the application of cytology in cancer diagnosis until 1939, when he fortuitously became associated with Dr. Herbert Traut of the Cornell Department of Gynecology and Obstetrics. Dr. Joseph C. Hinsey, who was head of the Cornell Department of Anatomy at that time, recalled later the historical circumstances of this association.

He came to me one day to get approval for a grant of some \$4,000 from one of the pharmaceutical firms to support a project in endocrinology. He was somewhat taken aback when I urged him not to take it, but instead to devote all his time to developing his cytologic method for diagnosis of early cancer in the reproductive tracts of women. I told him then how I had been impressed by his work first reported in 1928. He told me of his previous disappointments and his fears about securing adequate support and sufficient clinical material. The American Cancer Society was not then as vigorous as it is today and Federal programs for research support had not been begun. I assured him of my whole-hearted support and we both agreed that he should proceed step-wise, (1) to develop the method and establish its validity, (2) to train others to use it, (3) then to educate the profession and the public as to what it had to offer. The matter was then discussed with the late Dr. H. J. Stander, who was then head of Obstetrics and Gynecology in our Center. He encouraged Dr. Herbert F. Traut to intensify the work with Dr. Papanicolaou, a union which was a most fortunate one. Departmental funds were used until 1941, when the Commonwealth Fund, through Dr. Lester J. Evans, made its first grant of \$1,800. (44)

Reports of Dr. Traut's initial response to his association with Dr. Papanicolaou vary. By one account, Dr. Traut was actually involved in initiating the collaboration. "Traut stimulated it...and some early writings and...early ACS monographs of Traut and Ralph Benson [document this]." (45) By another account, Dr. Traut and his staff initially regarded Papanicolaou as "that crazy Greek who thought he could tell cancer by looking at the cell." By this same account, some of the resident staff who were providing smears to Dr. Papanicolaou soon became convinced that he actually "had something" and, in turn, Dr. Traut soon became very enthusiastic about Papanicolaou's work. (46) In any event, according to Dr. Charles Cameron, who was later to be Dr. Papanicolaou's chief advocate within the American Cancer Society, Traut's eventual enthusiasm stemmed directly from the fact that in his gynecological consultations he found Papanicolaou's work to be "fantastically accurate" in diagnosing cervical cancer. (47)

In 1943, four years after their joint work began, Papanicolaou and Traut published their now famous monograph entitled "Diagnosis of Uterine Cancer by the Vaginal Smear." (48) Their first joint paper appeared in 1941. (49) This collaborative work proved to be the turning point for the acceptance of the Pap smear technique by gynecologists. The monograph gave a detailed and illustrated account of collection, preparation, classification and interpretation of various cells found in the vaginal fluid and provided evidence that the vaginal smear technique yields a high percentage of correct diagnosis when checked with biopsies.

The work of Papanicolaou and Traut attracted the attention of others, particularly gynecologists, and before 1943 had come to a close, the first independent report supporting the value of the Pap smear as an adjunct to

diagnosis was presented by Meigs, Graham, and Fremont-Smith in Boston. (50) Further corroboration was presented in 1944 by Jones, Neustaedter and MacKenzie in New York (51) and by J. Ernest Ayre in Montreal. (52) Subsequent confirmation by routine smears in a larger series of cases was forthcoming within another year. (53,54)

The persistence and conviction of purpose of those who were the first to utilize the Pap smear is brought out in a biography of Ruth Graham, recounting her work with Dr. Joseph Meigs.

Maurice Fremont-Smith, impressed by an article written by George N. Papanicolaou, showed the article to J. V. Meigs, who thought the method would be worth trying. They chose Ruth Graham to investigate the technique. She read the article, then spent a week visiting the laboratories of Ephraim Shorr and Papanicolaou. [Shorr had been working with Papanicolaou on using vaginal smears for hormone studies.]...Mrs. Graham returned to Boston and began the collection and examination of smears. Apart from the interest of Dr. Meigs, her work attracted little attention.

Ruth Graham continued the examination of smears for more than a year. One day Dr. Meigs was performing hysterectomies on two patients, both of whom Mrs. Graham had found to have positive vaginal smears. The hysterectomies were for a fibroid uterus in one case and endometriosis in the second. After removal of the first specimen, Dr. Meigs called Mrs. Graham to the operating room, showed her the normal-appearing uterus, and demanded, "Where is the cancer?" Having the courage of her convictions, Mrs. Graham replied, "It must be there; there were malignant cells in the smear." Meigs made no reply, but proceeded with the second hysterectomy. Upon removal of this second benign-appearing uterus, Mrs. Graham was again called to the operating room and the interchange was repeated. Meigs was quite distressed, saying that he would be the laughing-stock of the hospital. However, subsequent histologic examination of the specimens confirmed the diagnosis of malignancy in each case, both patients having had in-situ lesions of the cervix. The accuracy of the cytologic method in these two cases convinced Meigs that the method was definitely valuable. (55)



Although it lacked the drama of other twentieth century medical advances, Papanicolaou's breakthrough--the development of a cytologic technique utilizing vaginal smears as a practical method of diagnosing asymptomatic uterine cancer--was ultimately to have a potential life-saving impact which may in time be acknowledged as surpassing in importance even the Salk and Sabin antipolio vaccines.

In retrospect, the principal factors impelling Papanicolaou forward were few in number. One important factor was the momentum gained through the association with Dr. Traut. The importance of this event was underscored in an interview with Dr. David Wood, a well-known pathologist whose influence on cancer research and control spans the past quarter century.

I think in all fairness, although this is known as a Pap test, we must not forget Dr. Herbert Traut because, except for Dr. Traut and the clinical sciences, maybe the Pap test would never have surfaced. It took the clinician and his enthusiasm to get it going. (56)

Apart from the good luck of Dr. Hinsey's interest, leading to the association with Traut, there was little extrinsic encouragement for Dr. Papanicolaou. Indeed, in sorting through the evidence, it appears that the success which Papanicolaou finally achieved was attributable mainly to his tireless work regimen, his technical resourcefulness, and his abiding belief in the inherent value of his work.

Not only was there little professional encouragement for Dr. Papanicolaou, but apparently his long tenure at Cornell University, dating back to 1914, was a source of considerable unhappiness and frustration. The record indicates that although Dr. Papanicolaou was at Cornell until shortly before his death in 1962, he did not receive an appointment as a full clinical professor until 1947--more than three decades



after he began his association with the University. (57) Dr. Koss comments, "Although Cornell, today, is bragging endlessly about what Dr. Papanicolaou did there, they really gave him a very hard time." (58) Dr. Heller, the Director of the National Cancer Institute at the time, offered these related observations:

I knew Papanicolaou personally and used to visit him, talk with him, and encourage him. He needed lots of encouragement because he had a lot of discouragement.... He never really became part of the family there for reasons not clear to me. He was regarded as somewhat of a fantastic figure who was playing around the fringes. This impression was probably primarily due to the pathologists....He was not in the bosom of the pathology family over there, and perhaps of the entire structure of the Cornell Medical College. (59)

Dr. Heller's statement that Papanicolaou "never really became part of the family [at Cornell]" is consistent with the views of others who knew Papanicolaou well during this period. Dr. Papanicolaou was a foreigner who, apparently, never managed to fit in with the aristocratic tradition so well established at Cornell.

#### Establishing the Role and Use of Cervical Cytology

The first studies of the vaginal smear were directed toward establishing its effectiveness in uterine cancer diagnosis. (The first applications in mass screening were to follow shortly.) After it was shown that some cases were being diagnosed primarily on the basis of the Pap smear, investigators began to advocate its use on a routine basis as a complementary technique in cancer diagnosis. Throughout the middle and late 1940s, clinicians directly responsible for patient care took the initiative in urging the expanded study and use of cervical cytology as an adjuvant in diagnosis and as a possible technique for screening. Meanwhile,

pathologists, a group that might be expected to take an active investigative interest in all potential methods of cancer diagnosis, tended to be skeptical and unwilling to participate in study of the role of cytology in diagnosing cancer. As expressed reflectively by Dr. Charles Cameron:

[T]he leading pathologists were still of the opinion that this was a flash in the pan and not to be taken any more seriously than any aspirate was of the vaginal fluid. (60)

The caution on the part of pathologists to endorse cytology, and their alleged influence in hindering the general acceptance of it as a complementary technique in diagnosis, was expressed in 1949 by Dr. Kano Ikeda, himself a pathologist at the University of Minnesota:

[M]any conservative leaders in the field of pathology who direct the minds of the average practicing pathologist, have taken a wait-and-see attitude and have been somewhat hesitant to wholeheartedly endorse the Papanicolaou method of cancer diagnosis as being worthy of adoption in routine work. They seem to view it with the academic interest of a skeptic, rather than with the open and practical mind of a clinical pathologist. They emphasize their preference for the older, more positive and reliable, though less spectacular, biopsy procedure, on the ground that the latter is a tried and established institution, not to be intruded by a seemingly questionable method of diagnosis by cell morphology alone, a practice so long frowned upon by them as unscientific and inaccurate. They probably see a parallel between it and the interesting observations of MacCarty's on the malignant cell, although the latter was dealing with the individual cells of fresh unfixed tissue. They are apprehensive, too, lest the new technique should replace the biopsy in cancer diagnosis, and thus the universal demand for its use to the practical exclusion of the more reliable histologic method of diagnosis might result. Furthermore, they are fearful lest the cytologists and technicians who are being taught to do the preliminary screening of the smears, might be encouraged to venture into the field of cancer diagnosis. Unfortunately, too, the popular acclaim given the method, through the medium of lay magazines, has tended to discredit its scientific value. The proposition that it might be used as a simple screening test by public

health agencies may have caused an unfavorable reaction. Thus, while the pathologist was still biding his time, the clinician, particularly the gynecologist, took the initiative in the investigation and evaluation of the method (for the simple reason that he has a personal interest in his patients) and contributed largely in its development and popularization. The clinician, and not the pathologist, has furnished the leadership in the application of this method in practice even though it is essentially a laboratory procedure, and the responsibility for the final diagnosis should rest with the pathologist. (61)

Dr. Wood, reflecting back on this early period, discards the notion that pathologists did not recognize the potential of cervical cytology and offers an explanation for the caution of pathologists:

The top academic men in the country saw the potential here and they realized that we were going to be faced with all sorts of individuals who were going to work this thing for profit.

The cautious included those who felt there was merit but that we had to have top quality personnel, M.D.s and technicians, and adequately equipped laboratories....They [varied] in degrees of cautiousness determined by doubts as to whether or not quality control was ever going to be attainable.

We knew that we had to train not only cytotechnicians but we had to train pathologists that had become familiar with [cytology]. [Manpower] was one of the big stumbling blocks that took us probably eight or nine years to get worked out. (62)

This concern on the part of pathologists for adequate training for all those engaged in cytology is underscored in a 1956 article by Drs. Lapid and Klemperer of the Mount Sinai Hospital in New York.

How, then, can a pathologist who has spent years of schooling, of specialized training, and of clinical experience associated with this specialty react toward the neophyte who invades his domain? There must be an emotional fear and resentment on the part of the pathologist toward the cytologist. How can these meagerly trained persons be so blunt in their diagnosis when, at times, the diagnosis cannot be made from submitted tissue? Still, this occurs with increasingly



better results as the incidence of false positive cellular smears decreases. (63)

The paper is entitled, "Teamwork Between Pathologists and Cytologists," but as the authors note it could have been made a short paper by writing under the title only one statement: "Teamwork there should be, but it is not always maintained." (64)

In spite of the extreme caution or resistance on the part of pathologists generally, the utilization of the Papanicolaou smear continued to go forward, first as an adjunct to diagnosis and, then, as a procedure for systematically screening asymptomatic women. Although involving only small populations in single institutions, reports on the use of vaginal cytology for screening were already forthcoming by 1947-1948. (65,66,67,68,69,70) One of these reports dealt with a long-range study initiated in January, 1945, by the Massachusetts Department of Public Health to evaluate its use in a statewide program. (71) The study was begun in part because of a suggestion by Dr. Meigs and his associates in their 1943 paper that the diagnosis of vaginal smears should be available to all physicians through the Massachusetts Department of Public Health's Tumor Diagnosis Service. The study's purpose was "to determine whether this [Papanicolaou] test is of sufficient value to warrant its use in the [18 Massachusetts State] cancer clinics as a screening test to detect symptomless carcinoma or as a routine diagnostic measure for all gynecologic cases and, secondly, whether it should be offered to all physicians in Massachusetts as another form of tumor diagnostic service." (72) "[It] was the first large scale study of the use of Pap screening as far as a cross-section of the female population was concerned." (73) In a preliminary report on this study in 1948, Dr. Herbert Lombard and his associates made the following observations:



[T]he use of the method has been limited, owing in large part to difficulties of interpretation of smears and the time and training required for competence in diagnosis. The pressure of public demand resulting from recent publicity of the vaginal-smear technique has prematurely forced an answer to the question of its practicality both as a routine diagnostic method and as a screening test.

It should not be supposed that an experienced pathologist or cytologist can successfully undertake the interpretation of smears without acquaintance with the manifold variations of the structure of exfoliated cells in cases of pelvic disease and neoplasia....It will take from four months to a year to gain proficiency in this type of diagnosis, depending on aptitude and richness of material available for study. (74)

In regard to the evaluation of the method as a widely used diagnostic measure Lombard and associates stated:

Despite the initial difficulties and expense involved in the diagnosis of smears the method appears to be peculiarly suited for large-scale use. The limiting factor at present is the availability of technical skill. (75)

Dr. Paul Younge, in 1950, advanced the view that cervical cancer can be found before it reaches its symptomatic state, but only if screening is carried out routinely.

In spite of the recent advances in exfoliative cytology and the recognition of carcinoma in-situ as the early stage of squamous cell carcinoma of the cervix, it still remains a fact that the great majority of women who are treated today for cancer of the cervix already have symptoms for which they seek medical aid. When cancer of the cervix first produces its classic symptoms of abnormal bleeding and a change in the type of vaginal secretion, it almost invariably is an invasive lesion and not infrequently a fairly advanced one. (76)

Dr. Younge referred to work by Pund and Auerbach (77) in reaching his conclusion on the necessity of Pap test screening.

Pund and his associates believe that cancer of the cervix does not become obvious for as long as six years after microscopic invasion takes place and that carcinoma

in-situ exists for nearly six and one-half years before it invades microscopically.

During this symptomless stage in the development of cervical cancer, Papanicolaou smears and selective cervical biopsies with the help of the Schiller Test will reveal the disease when it is nearly 100% curable. Consequently, women must have adequate pelvic examination routinely and not just because of symptoms. (78)

In spite of less than complete consensus among the medical community, the momentum for using the Papanicolaou test for screening as well as diagnosis was firmly initiated during the immediate post-World War II period. However, the value of cytology in screening was slower in gaining recognition than its utility as an adjunct to diagnosis, probably because in screening of asymptomatic populations initial decision-making on whether further diagnostic work-up was indicated would be made frequently on the basis of cytology alone. It was particularly difficult to get pathologists to accept this critical role for cytology. Even among clinicians there were instances where the utilization of the Papanicolaou smear was supported not because of its direct contribution to detection of early cancer but because of its indirect contribution as an education tool. Dr. John K. Kernodle, in 1948, reflecting on the experience in the obstetrics and gynecology clinics at Duke University referred to this "spinoff" of the Papanicolaou test. When physicians begin to take Pap smears then "physicians will be required to do more pelvic examinations... and ...the combination of both will result in early detection of malignancies." (79)

As part of the increased interest in early cancer detection that was possible through use of the Papanicolaou smear, cervical cytology was slowly being established in physicians' offices. The assumption was that routine examination and screening were now possible when combined with

the ability of a cytologic specialist and a laboratory to offer a detection service to an entire community. It was felt that the addition of cytology required relatively little additional skill on the part of the examining physician. Particularly notable efforts in three different geographic areas, Toledo, San Diego, and Vancouver, were getting under way in the late 1940s. These efforts led to large-scale organized programs centered around the involvement of community physicians. The goal of each was the testing of a practical method for mass population screening.

The Academy of Medicine of Toledo and Lucas County, Ohio, established a community-wide program in 1947 for the detection of uterine cancer. (80) Women were urged to go to their own physician once a year for a history, pelvic examination, and a vaginal pool and cervical scrape smear. All Lucas County pathologists were involved in reading the slides which were sent directly to them by the examining physician. The patients paid for all costs except those associated with a data collection and analysis center operated by the academy and funded through local ACS grants and the Cancer Cytology Research Fund of Toledo. (81,82)

In San Diego, California, Dr. Purvis Martin initiated in 1949 a routine cervical cytology screening effort in his gynecologic practice. (83) About a year later he and seven other gynecologists formed an association and established the Gynob Laboratory with a trained cytotechnician in charge who screened all smears. This laboratory service was also made available to other physicians who wanted to send slides there. For \$3.50--the cost of preparing and examining the slide--the patient received a statement directly from the laboratory. As screening expanded in the area, project coordination was assumed by the San Diego County Medical Society's Uterine Cancer Control Committee. (84)



In the Canadian Province of British Columbia, a cytological diagnostic laboratory was established in 1949. This central laboratory, which is still in operation, provides free service (processing and interpretation of smears) to all offices of private physicians practicing throughout the province. The purpose of the laboratory is to encourage the use of cytology in detection of cancer in its early stages and thereby reduce the mortality in an entire region. (85)

In addition to these activities on a regional level, events on a national scale were also beginning to take place which had a significant influence on the expansion of cervical cytology. In fact, the degree to which cytology was disseminated throughout the United States during the 1950s and 1960s depended to a great extent on the influence of various groups and organized efforts. Large-scale efforts generally require the involvement of national organizations. Professional societies, organizations, and federal institutions were all influential in setting the pace of progress during this period.

The American Cancer Society played a key role in the development of cytology. For example, the ACS was instrumental in providing the first multidisciplinary forum for addressing the issues that pathologists had raised about cervical cytology. According to Dr. Papanicolaou's 1958 recollection:

The swift expansion of the cytologic method in its use in the diagnosis of cancer was due in large measure to the endorsement and support given to it by the American Cancer Society and the United States Public Health Service.

The first Cytologic Conference, which was held in Boston in 1948, was organized under the sponsorship of the American Cancer Society. It was then that cytologists and pathologists had their first encounter around a conference table. The ensuing enlightening discussion paved the way



for a better understanding which has since developed into close cooperation and friendship between these two groups. (86)

This 1948 Cytology Conference proved to be a turning point in addressing the cautious attitude held by pathologists and, consequently, extending the general utilization of cytology within the medical community. The initiative for the conference came from within the American Cancer Society and, specifically, from Dr. Charles Cameron who recently recounted the events leading to the conference.

[A]s a result of my conversations with Dr. Papanicolaou and discussions with people whom I really regarded highly, like Howard Taylor and Joe Meigs, who was doing superb work with Ruth Graham in Boston, I got the idea that this was a great opportunity to save lives. So I pushed the Cancer Society for backing this full tilt. We put it in our publications for doctors and we made much of it for the laymen by means of films [and] pamphlets. I wrote some public affairs pamphlets about it. Well, the cumulative effect was that it gave way faster than I think it otherwise would have. In 1948 I called the first National Conference on Cytology. We called it at the Somerset Hotel in Boston and we invited 100 people and we paid their way. We divided them as nearly as we could between those who were for it and those who were skeptics or against it. And it was a lively argument for the two days of the conference. I think that perhaps did something to persuade the people that it was here to stay. (87)

This momentous event addressed a number of factors which required attention if all interested parties were to work together in the systematic and orderly expansion of cytologic diagnosis. Eight resolutions were adopted by the delegates to the conference that gave specific attention to such factors as: criteria for interpretation of exfoliated cells; biopsy confirmation; training facilities; uniform data collection and reporting; the establishment of a registry of exfoliative cytology; and the need for discouraging premature publicity. (88)

An important subsequent step in helping to bring clinicians and pathologists together on a national level was the creation of the Inter-Society Cytology Council. (89) The purpose of this group was to foster the widespread application of the cytologic method in a manner that would be acceptable to all. The establishment of this Council was not without some planning difficulties. The original idea for an organization of this nature was first conceived in 1949 and out of it came the Cytology Institute, an organization chartered in the state of New York. However, as Dr. Meigs stated:

As chairman of the Cytology Institute, I found it impossible to interest a sufficient number of key people [including Dr. Papanicolaou] in the organization as it was constituted at that time. (90)

As a result, an entirely new group was invited to consider the problem and from them came the recommendation for the Inter-Society Cytology Council. This new group became the "Founders' Executive Committee" and included Drs. Meigs, Papanicolaou, Cameron (of the ACS), Kaiser (of the NCI), and others.

To achieve a general acceptance of cytology, it was apparent to the Founders' Executive Committee that the responsibility for cytology would have to be shared between clinicians, cytologists, and pathologists. The clinician would be responsible only for collection of the smear; the ability to stain and interpret these smears would be reserved for a cytologist or a cytopathologist (and not a cytotechnician); and the confirmation of a cytological diagnosis by interpretation of a biopsy specimen would be done by a pathologist. (91)

Neither the cytologist, pathologist, nor clinician can utilize the method effectively without the help and cooperation of the other two. A jack-of-all-trades-and-master-of-none should have no place in the cytological

picture and has no place in the Inter-Society Cytology Council. (92)

The Council went on to state as one of its initial aims:

To establish standards, acceptable to presently acknowledged cytologists and cytopathologists, for individuals who want to be recognized as qualified cytologists, cytopathologists, or cytotechnologists (screeners). An essential part of the function of the Inter-Society Cytology Council is to insure the thesis that no one be certified to render a cytological report unless his qualifications are recognized and established. This is to prevent exploitation of the methods by unscrupulous individuals and by those not qualified to render accurate reports. It is intended, also, to provide a stimulus to maintain acceptable standards of teaching and training by institutions engaged in this type of program. (93)

The establishment of the Inter-Society Cytology Council proved to be an important milestone in improving relationships between medical specialties interested in cytology. As expressed by Emerson Day of the Sloan-Kettering Institute's Strang Cancer Prevention Clinic, in speaking on the accomplishments and shortcomings of cancer cytology in 1956:

Perhaps the most important general accomplishment has been cytology's coming of age during the past five years. ...The progress can be attributed to the persistence of cytologists, the understanding of many pathologists, and the accumulating experience of clinicians. The feuding that muddled the field seems to be largely over....The new cooperation is best demonstrated by the Inter-Society Cytology Council....(94)

However, the problem of an inadequate number of manpower trained in cytology with corresponding facilities was still not resolved by 1956.

The major shortcoming of cancer cytology at present is the gross inadequacy of laboratory facilities for reliable cytological services, both screening and diagnostic....While there are a number of communities where an effective program has been established, too often cytology is unused because it is not readily available or, if offered, is not maintained at a reliable level.... The immediate need is for a substantial increase in the number of technicians trained in screening and of pathologists experienced in cytodiagnosis. Once staffs



are available, there must be laboratories prepared to render reliable cytologic reports at strategic points throughout the country. In order for such a regional program to reach a satisfactory level of achievement, it will probably require the aggressive support of such organizations as the American Cancer Society and the National Cancer Institute, and the guidance of a body such as the Inter-Society Cytology Council. (95)

The shortage of adequately trained manpower was a definite force in restraining the expansion of cytology and the American Cancer Society was involved in an early stage in helping to overcome this obstacle. As early as 1948 it was offering clinical fellowships in exfoliative cytology to physicians trained in pathology. (96) That the increasing demand for cytologic service was always several steps ahead of the capability of facilities and manpower to provide the service is evident from two representative reports in the late 1950s.

Cytologic diagnosis of uterine cancer has recently gained the attention of many lay magazine and newspaper editors, resulting in a public demand for something which the medical profession is not ready to provide. (97)

The most serious handicap in the wider utilization of exfoliative cytology in the diagnosis of cancer is perhaps the lack of an adequate number of well trained cytopathologists and cytotechnicians. Such training requires proper instruction and study in a qualified cytology laboratory for a period of at least one year. (98)

In a paper nine years earlier which corroborated the 1948 ACS conference training resolution, Dr. Papanicolaou stated that a training period of at least three months but preferably six months was sufficient to gain skill in the technique and interpretation. (99) Apparently, as time went on, it must have become evident that the complexity of training was greater than initially anticipated.

From its early support of training to the present time, it is clear that the force of the American Cancer Society has been important in



furthering the use of cervical cytology. Both on a national level and through its state divisions, the ACS has been instrumental in providing the support necessary for establishing numerous cytology screening programs and cancer detection centers throughout the United States. (See Book Two, Chapter 10.)

The National Cancer Institute also contributed substantially to the development of cervical cytology. Fortunately, the rapport between the ACS and the NCI was such that the activities of one complemented the other. As stated by Dr. Cameron: "The collaboration between the ACS and the NCI was firm and established early, and I think that a lot of it was due to our sense of mission and to our compatibility as individuals." (100)

NCI became involved in advancing the application of cytology to detection of cancer through the establishment of its Cancer Control Branch in 1947. (See Book Two, Chapter 4 .) This Branch, under the direction of Dr. Austin V. Deibert, set up a cancer detection clinic in November, 1947, in conjunction with an existing treatment center for venereal disease, in Hot Springs, Arkansas. (101) In 1951, Dr. Raymond F. Kaiser assumed the leadership for Cancer Control within the NCI, and the Branch turned its attention to demonstrating the application of cytology to detection of cancer in large population groups. As Dr. Kaiser noted, the usefulness of the Pap test as an adjunct in the diagnosis of cervical cancer had already been demonstrated by then. (102) As a result, the Branch turned its attention to gathering epidemiological information and testing the practicality and efficiency of the Pap test in screening general population groups, and the NCI in 1952 established its first large-scale demonstration project in cooperation with the University of Tennessee in Memphis - Shelby County. (103,104,105)

The original proposal for initiating the Shelby County project came from within the NCI itself. (106) Dr. John Dunn, an epidemiologist within the Field Investigations and Demonstration Branch, developed the proposed project after discussion with Drs. Sprunt and Erickson, pathologists at the University of Tennessee. Dr. Dunn recognized that the success of the project was dependent on "bringing something to the medical community and getting them to accept it." Memphis was chosen because of Dr. Sprunt's ability as an organizer and his "political savvy." Dr. Douglas H. Sprunt was able to propel the project in spite of resistance from within pathological quarters of the medical society. (107)

Beyond its demonstration purposes and its being a means for evaluation of the sensitivity and specificity of the test, an important component of the project was to investigate the link between carcinoma in-situ and invasive cancer.

Because experience with vaginal cytology has raised a number of questions regarding the morphogenesis of cervical cancer, the answers to which will have a direct bearing on the use of the procedure for case finding, it is important that this experience be gained in a carefully planned study designed to take cognizance of these questions and secure answers where possible. (108)

Pathologists around the country were reluctant to take a research interest in cytology, and the Shelby County project was seen by its architects as a means to study carcinoma in-situ without them. Dunn concluded, "Cytology was something in which they didn't want to have any part and not having been trained in cytology themselves, they claimed that it was not possible to diagnose cancer without tissue." (109) Dr. Lewis Robbins expresses a similar view on the reluctance of pathologists to take an interest in carcinoma in-situ and in cytology as a means to study the natural history of cervical cancer.

The Pap smear isn't diagnosing cancer, it's diagnosing a precursor. Why do they call it cancer then? Because nobody would pay any attention to it when they would call it a dysplasia....If you call it carcinoma in-situ then they will examine it, do something with it.

I remember a battle royal at Roswell Park in 1946. Three men got together, then five, then six, right in the hall. The pathologist was saying that the Pap smear is no good. But [one physician in the group] said carcinoma in-situ is not a cancer but we have to call it cancer. The pathologist said we can't call it cancer if it doesn't metastasize or if it hasn't already metastasized. Well, they did. (110)

It should be noted that not all pathologists were disinterested in studying carcinoma in-situ and its relationship to invasive disease. The significance of carcinoma in-situ was reviewed in 1952 by Drs. Arthur T. Hertig and Paul A. Young, pathologists at Harvard Medical School. (111) For both in-situ and invasive disease, they reviewed evidence relating to incidence, age distribution, selective racial incidence, biologic behavior, histologic appearance, and exfoliative cytology. Their study supported the statement that "carcinoma in-situ is the preinvasive stage of squamous carcinoma of the cervix." (112) However, they acknowledged that "final proof was lacking as to whether untreated carcinoma in-situ inevitably goes on to invasive disease" and that "morphological criteria of preinvasive cervical lesions need clarification and standardization in order that such lesions may be properly diagnosed and treated." (113)

The operation of the Memphis-Shelby County project differed from the two other large-scale projects in San Diego and Toledo. Because they involved primarily private patients, the latter two projects relied to a greater extent on physician involvement than was true in Memphis. The San Diego project used cytotechnicians to examine smears, but in Memphis



technicians and nurses were involved also in taking the specimen and in some cases examining the cervix in clinics for indigents. (114) According to Dr. Dunn:

A lot of the population wouldn't have the means to go to a physician to have this done, so we had to have clinic facilities for these people. [A vaginal pool aspiration smear and not a cervical scrape smear was generally the only sample taken from these patients.] That is what we were using because we knew the physicians would not allow a nurse even, and certainly not a technician, to use a speculum. This is a medical procedure that they were not about to turn over to any nonmedical people. That is how we got into this vaginal cancer specimen as the kind of specimen to use. (115)

Throughout the project the emphasis was on using non-physicians; in most cases, the cytology labs were staffed with technicians hired by the NCI for the project. Other NCI staff members were provided to supervise training of cytotechnologists, evaluate the program, and provide technical assistance not otherwise obtainable in the Memphis area.

Although initially planned as a three-year program, (116) this support tactic absorbed human and budgetary resources for many years. According to Dr. Raymond Kaiser, in charge of this and other federal Cancer Control projects:

The thing kept growing by leaps and bounds. Dr. Sprunt was a nice guy...but he had delusions of grandeur. He was going to have a second Cancer Institute down there. The only difficulty about that study was that while it took a certain amount of endeavor to initiate it, it took ten times that amount of endeavor to get it stopped. (117)

After more than nine years of steady and ample support, the NCI wanted to terminate the "demonstration." Kaiser believes that at one time as many as 80 of the project staff were federal civil service employees. Sprunt "moved everything except Congress," and the project did continue for several years more. (118)



Louisville, Kentucky, was the site of another large-scale screening program that was initiated with support of the National Cancer Institute. This program was started in 1956 by the NCI and the University of Louisville School of Medicine "in an area where essentially no cervical cytology was performed." (119) It was directed by Dr. William M. Christopherson, a pathologist at the University, and as he stated in a preliminary report on the program in 1962:

The purpose of the study was to screen the female population of Jefferson County, Ky., for cervical cancer and to repeat screenings at yearly intervals on as many women as possible. Since funds were never a limiting factor, any degree of success was a measure of the interest the physicians and lay population developed in trying to eradicate death from cervical cancer in our community. (120)

Thus, the NCI had in the five years since the design of the Memphis project turned its attention from demonstrating feasibility to that of demonstrating impact on mortality.

The Jefferson County program was started by providing a central laboratory as an integral part of a community-wide program of population screening, in an area which had little or no previous screening. As with the Memphis project, NCI staff were at the site full time. Soon private laboratories became attracted to providing cytology service and by July, 1960, the central laboratory became a separate operation concerned only with medically indigent patients. Private patients were examined by their own physician and the cytology was done by the pathologists practicing in the community. (121,122) By 1967, over 90 percent of the adult female population had been screened at least once (123) and a significant drop in cervical cancer mortality was attributed to the mass screening effort. (124)

During the time that the Memphis and Louisville projects were ongoing, other projects were supported in other cities to further assess the value and feasibility of exfoliative cytology methods in the detection of uterine cancer and to assess the incidence of genital tract cancers in different population groups. As a result, in addition to 42 people in Memphis and 28 in Louisville in 1957, the NCI had 29 personnel stationed in Columbus, Ohio; 14 at the Madison, Wisconsin unit; seven in Philadelphia; two in San Diego; and 21 at the Washington, D.C. unit. (125) By providing personnel and financial support for data management to these and other projects, the NCI was able to encourage a certain uniformity in procedures and standards and thereby facilitate comparison of results among projects. (126)

Some of the major cytologic screening projects that were established during this time period are identified in Table 2.

Table 2

Major Cytological Screening Surveys  
for Cervical Cancer\*

Investigator	Place	Time	Age	Race
Calabresi, et al. (127)	Madison, Wis.	1947-56	20+	White
Burns, et al. (128)	Toledo, Ohio	1947-63	18+	White
Quisenberry (129)	Hawaiian Islands	1949-61	Adult	White & Nonwhite
Dunn, et al. (130)	San Diego, Ca.	1950-55	Teens+	White & Nonwhite
Nieburgs, et al. (131)	Floyd County, Ga.	1951-55	Teens+	White & Nonwhite
Kimmelstiel, et al. (132)	Charlotte, N.C.	1951-56	Teens+	White & Nonwhite
Kaiser, et al. (133)	Shelby County Memphis, Tenn.	1952-57	20+	White & Nonwhite
Stern (134)	Los Angeles, Ca.	1955-58	20+	White
Miller & von Haam (135)	Columbus, Ohio	1956-59?	Adult	White & Nonwhite
Christopherson & Parker (136)	Jefferson County Louisville, Ky.	1956-68	14+	White & Nonwhite
Bibbo, et al. (137)	Chicago, Ill.	1959-69	Teens	White & Nonwhite
Figge, et al. (138)	Seattle, Wash.	1962-68	Adult	White?
Davis & Jones (139)	Washington County, Md.	1963-65	30-45	White

\*Adapted from Kessler, I. I. and Aurelian, L. (140)

As the 1960s approached, the nature of the federal participation shifted away from direct involvement in providing technical and financial assistance in running screening programs. Instead, emphasis was placed on the stimulation of organized programs within health care delivery settings which were already established. The participation of private practitioners was enlisted through the initiation of the Office-Detected Cervical Cancer Program. (See Book Two, Chapter 6.) Dr. Lewis Robbins, who headed the federal Cancer Control Program at the time, later characterized the Office-Detected Cervical Cancer Program as "the most important thing that was done in all of cancer control." (141)

Methods of Obtaining and Processing Cytologic Smears: The Question of the Self-Obtained Smear; the Question of the Cytoanalyzer

Beyond demographic differences in the populations screened, there are also differences among screening programs in the type of smear taken. In an early report on experience gained in using cervical cytology to diagnose cancer, Dr. Papanicolaou identified four types of smears which he was requesting at that time: vaginal aspiration, cervical or endocervical aspiration, direct cervical smear taken by a cotton swab or wooden spatula (scraping), and the endometrial aspiration smear. (142) The cervical spatula smear method was introduced in 1946 by J. Ernst Ayre. (143) Two of the methods, the vaginal aspiration and the direct cervical smear, were the most commonly used in the cytologic screening programs which were established. The vaginal aspiration smear can be obtained by technicians and is, therefore, well suited for mass screening. However, many clinicians think that preclinical or early cancer of the cervix is unlikely to exfoliate many cells into the vaginal pool and thus prefer a direct cervical



smear as a means to detect cervical cancer early in the disease course. (144,145) Today, the following procedure of obtaining a cytologic smear is considered routine:

By means of a cotton-tipped applicator moistened with saline and rotated in the endocervical canal, obtain endocervical cells and smear them on half of a clean glass slide. Then, lightly scrape cells from the squamocolumnar junction with a wooden spatula and smear them on the remainder of the slide. Immediately fix the smeared cells by placing the slide in a mixture of equal parts ether and 95 percent alcohol. Drying before fixation will invalidate the smear. Exfoliated cells from the cervix and endometrium may also be obtained in a specimen from the vaginal pool. (146)

The cervix smear is obtained by the physician at the time of the gynecologic examination. Only the vaginal smear, which is not considered mandatory when a cervical smear is available, could be obtained otherwise. A logical question arises whether the vaginal smear might be obtained by the patient herself, particularly in those women who do not receive examinations. This point was addressed almost simultaneously with the first applications of the Pap smear. In fact, in their monograph, Papanicolaou and Traut suggested that women could be taught to obtain their own smears. (147) Drs. Gates and Warren in a report published in 1945 stated, "The method is simple and if necessary may be performed by the patient." (148)

Thus, the possibility of self-obtained smears was recognized early. However, the dominant issue in the cytology controversy during the 1940s and 1950s was the role and efficacy of cervical cytology itself, and not the method of obtaining the sample. It seems that it was generally assumed that the specimen would be obtained by a physician or at least by a paramedic. Nevertheless, as mass screening increasingly became a realistic goal, further attention was given to self-obtained smears. In 1954, Dr.

Alexander Brunschwig of the Memorial Center for Cancer and Allied Diseases reported on the development of a special tampon designed for self-obtained smears (and manufactured by the Tampax Corporation).

It would appear that mass screening should be greatly facilitated were it possible to secure adequate smears with minimal employment of professional personnel and with minimal effort and expenditure of time on the part of the subjects to be screened. In conjunction with Andre Draghi it was decided that the principle of utilizing a vaginal tampon that could be self-inserted and that could afford satisfactory material for smears would be worthy of trial. (149)

Dr. Papanicolaou consented to study the smears obtained by this method and evaluate their quality for diagnostic purposes. Although he noted some difficulties, particularly in terms of the adequacy of the uterine secretion obtained by the tampon method, he stated that the method "appears to be suitable for mass screening purposes." (150) However, comparative evaluation of self-obtained smears with standard vaginal and cervical smears resulted in differences in opinion. Badar and his associates reported results in 1957 suggesting that a self-obtained tampon smear was adequately reliable for screening purposes. (151) On the other hand, Scott and his associates pointed out that tampon smears present difficulties in the detection of early lesions. (152)

In 1962, Dr. Hugh J. Davis, a gynecologist at Johns Hopkins University, reported on the development and successful application of an improved method for self-obtained smears: a vaginal irrigation smear. (153) With this method the woman collects the specimen herself by using a plastic unit consisting of a bulb filled with cell preservative solution for irrigation and a pipet for aspiration of the vaginal sample; the entire unit is sent to a laboratory for microscopic examination of the sample. The results of a field trial were presented in 1966 by Davis and an associate. (154) They

noted that only a very small percent of the adult female population had been motivated into routine gynecologic examination and that if control of cervical cancer is to be achieved, some realistic way of reaching essentially the entire population must be developed. Furthermore, the means of accomplishing this must not require professional manpower beyond that available. They suggested that the irrigation method was a practical way to overcome both "the physician man-hour problem" and the "examinee motivational problem," and they presented field trial data to support their thesis. (155) Evaluation of the efficacy of the self-obtained irrigation smear has received considerable attention by other investigators, with mixed reports. (156,157,158)

Agreement has not been reached on the role of the self-obtained smear. Advocates point out that this may be the only method to reach certain population groups, and at a fraction of the cost. Others are concerned that the self-obtained smear may be used by some women as a substitute for a more complete gynecologic examination. Interestingly, the pathologists who so forcefully resisted the Pap test as a screening procedure, have evidenced no organized opposition to the self-obtained smears. Indeed, they likely stand to profit considerably from its widespread use. But gynecologists--those who were in the forefront of the struggle for mass utilization of the Pap test--have opposed the use of self-obtained smears, apparently fearful that it may become a substitute for a more complete office-visit gynecological examination. The basis for either acceptance or rejection of a detection method should be its efficiency. However, as pointed out by Dr. Koss, evaluation of a new method by comparing it with an accepted method which itself has not been fully evaluated creates obvious difficulties.



[W]hat people are trying to do is to say it's adequate or it's inadequate...[but] when compared to what...? You are comparing two unknowns to each other. People say the standard method is the cervical scrape, therefore, self-administered smears should be at least as good as the cervical scrape, and it's been proven that it is not quite as good. The question is now how adequate is the cervical scrape. (159)

One reason for advocating the self-administered smear is that it represents a way to overcome the problem of insufficient medical manpower that would result if screening examinations were done regularly throughout the United States. However, widespread screening, even if done using a self-administered method, would likely result in a shortage of technical help in the preparation and screening of smears.

Recognition of this, as early as the 1950s, led to interest in automation of slide interpretation. The NCI's Field Investigations and Demonstrations Branch (re-named the Diagnostic Research Branch in 1961) at its cytology laboratory in Hagerstown, Maryland, became involved in testing a cytologic screening instrument in 1958. (160) The instrument was developed by W. E. Tolles at the Airborne Instruments Laboratory, Inc. in Mineola, New York, with financial support from the Sloan-Kettering Institute and the American Cancer Society. (161,162) The instrument, called a cytoanalyzer, classified microscopic particles (nuclei of epithelial cells) into various categories on the basis of area and light absorption. The hope was that the computerized instrument could be used to identify negative smears which otherwise would require examination by qualified cytotechnicians. The first field trial of the cytoanalyzer took place during 1958-59 and, at that time, it was recognized that further improvements and study were necessary to overcome noted difficulties. (163) A second, more extensive field trial was conducted in 1959-60 and again only limited success could be reported. (164) At that time, it was pointed out that



further research and development were required in both the preparation and staining of the cytological material and in the instrument itself.

The cytoanalyzer project was discontinued by the NCI in 1961 and attention was directed toward the general problem of recognition, classification, and morphological analysis of normal and abnormal cells. (165) Building on previous instrumentation, a cytophotometer and data conversion system (CYDAC) was developed under contract by Airborne Instruments Laboratory for use in these quantitative cellular studies. During the mid-1960s, investigators at the University of Pennsylvania were supported to explore the potential of this "biological data collection system." (166)

Where has this effort in automation research and development led us? As expressed in a recent symposium on automated cytology by Dr. Gunter Bahr, Chief of the Biophysics Branch of the Air Force Institute of Pathology:

Serious efforts currently underway in a few laboratories will eventually produce machines for screening of cytologic and also of hematologic material. First there will be prototypes. Finally, finished products will be offered. The readers of this symposium are reminded to proceed with caution not only in procuring an instrument, but more so with respect to the premature release of trained staff. Only a full field test, carried out in the frame of the special conditions that often prevail in different laboratories, paralleled and compared to regular screening procedures by trained personnel can provide an answer to the usefulness and economy of a new device. Until such time, a fully operative screening machine is not closer, but also no farther away than a human landing on Mars. (167)

Although desirable, automation of cytology as a means of overcoming problems of insufficient manpower appears to remain a considerable distance in the future. As pointed out by Dr. O. A. N. Husain, Director of Cytology Central Group Laboratories at St. Stephens Hospital in London,

in repeat screening the yield of positives becomes extremely low, and, consequently, automation of cytology becomes increasingly important as a means of overcoming the sheer boredom which makes it more likely that the rare positive cytology may be missed. (168)

In summary, although the commonly used methods of obtaining cytologic samples, and the preparation of the slide and its interpretation, have improved over the past quarter century, major breakthroughs in promoting self-obtained smears, or in perfecting the cytoanalyzer, have yet to be realized.

#### Degree of Utilization and Evaluation of Efficacy

A fundamental question regarding cervical cytology still looms: To what extent has it been shown that cytologic screening reduces mortality from cervical cancer? In a recent review of cancer of the cervix one notes that despite the many separate programs undertaken, no controlled prospective study has been conducted. Furthermore, because of the present consensus that cytology is indeed effective, most agree that the day when a controlled study of the efficacy of any type of cervical smear could be carried out in the United States ethically, or practically, has passed.

The National Cancer Institute asked the question in a December, 1974 announcement of a request for proposals:

The Division of Cancer Control and Rehabilitation of the National Cancer Institute is soliciting proposals for a project to develop a means of measuring the effect of a well-run Pap screening program on the incidence and mortality of invasive cervical cancer in a community setting over a suitable period of time. A comparison will be made to incidence and mortality of invasive disease in a comparable population having access to whatever screening procedures are normally available to them to determine if

a well-controlled screening program has a greater impact on the incidence and mortality of invasive cervical cancer. (169)

After reviewing the proposals that were submitted by several institutions in response to the RFP, the NCI review committee determined that the study was not feasible. Thus, the answer to the question of efficacy will have to come indirectly through retrospective statistical inference relating utilization of cervical cytology to a decrease in incidence of invasive disease and mortality.

The time required for cytologic screening to have an impact on mortality is a major consideration in studies of efficacy. Cervical cytology can detect the disease at an early state (carcinoma in-situ) before the disease is clinically recognizable and thus a significant time lag will exist between the widespread use of cytologic screening and its eventual impact on mortality. This time lag may be as long as 20 years (and in some unusual instances as short as a year or two). The average duration of carcinoma in-situ has been estimated to be 11 years followed by another five years while the cancer is invasive but preclinical and asymptomatic. (170) This estimate is supported by recent data showing a 15.6 year difference between the mean age of patients with carcinoma in-situ and those with invasive cancer. (171) To this 16 years must be added the time between diagnosis of the disease in its invasive stage and death. For those patients who die from cancer of the uterine cervix, this additional time lag is relatively brief--two or three years. However, it should be realized that a sizeable proportion of all cervical cancers are cured even when invasive (172)--the 15-year relative survival is slightly greater than 50 percent--and thus the influence of mortality is not felt in the entire population of patients with invasive cervical cancer. All of



this suggests that the effect of cytology on national mortality rates will not become clear until 10 to 20 years after the majority of women started cytologic screening on a regular basis.

It should be evident that extensive longitudinal data are therefore needed on both the extent of cytologic screening and mortality. Mortality data are readily available, but only recently have there been reasonable, explicit, and accurate data on the utilization and penetration of cervical cytology. The earliest data reflective of the entire United States reaches back only to the early 1960s. Studies of the impact of screening on reducing the incidence of invasive disease (through detection and intervention at an earlier stage) are limited for these reasons. Accurate assessment of disease incidence requires total case ascertainment and is, therefore, difficult to accomplish. With a few exceptions (e.g., Connecticut) incidence data is not collected routinely for complete populations, and special surveys, such as NCI's National Cancer Surveys, are expensive and infrequent. Since the 1960s there has been only one survey.

The first national survey of cervical cytology utilization was conducted in 1961 by the College of American Pathologists and the American Cancer Society. (173) Subsequent surveys were made in 1963, 1966, and 1968 by the College and the Cancer Control Program of the U.S. Public Health Service. (174) The surveys were all similar and were based on a questionnaire mailed to each member of the College of American Pathologists. The response ranged from 65 to 90 percent and, after adjusting for non-respondents, an estimate was made of the number of cytologic examinations per 100 females age 20 and over. The rates of reported examinations for 1961, 1963, 1966 and 1968 were 10, 15, 26, and 25, respectively. It should



be recognized that these estimates may not represent a completely accurate reflection of the number of women screened for cervical cancer. The surveys contained information from only those laboratories that have a pathologist who is a member of the College of American Pathologists, and thus may have excluded a significant number of cytologies performed in commercial laboratories, state laboratories, and gynecological departments. The data can be considered only as a lower estimate of the true level of screening.

Data for the year 1973 are available from the National Center for Health Statistics (NCHS) using a different method of collection. The NCHS obtained its data from household interviews in a probability sample (120,000 persons) of the civilian, non-institutionalized population of the United States. (175) These data indicate that, in 1973, 46 percent of women 17 years of age or over had at least one Pap smear within a year of the survey.

Table 3 presents these data, which are representative of the extent of annual cervical cytology screening for the entire United States. Obviously, higher levels of screening can be expected in areas of the country where concerted screening efforts were undertaken. Two of these areas where published annual data on screening intensity were available are shown: one, discussed previously, is Memphis-Shelby County, Tennessee, where an aggressive, organized screening program was initiated in 1952; and the other area listed is Olmsted County, Minnesota (the location of the Mayo Clinic), where, without any particular organized "program," screening started early and continued to increase. For comparison purposes, data for Canada and British Columbia are shown.

Table 3: Intensity of Cytologic Screening for Cervical Cancer

<u>Examinations per 100 Adult Females</u>					
<u>Year</u>	<u>U.S.*</u>	<u>Shelby + County Tennessee</u>	<u>Olmsted + County Minnesota</u>	<u>Canada †</u>	<u>British † Columbia</u>
1952		8.4	1.5		
1954		24.4	2.0		
1956		29.7	7.2		
1958		20.0	16.3		
1960		21.0	20.8		
1961	10	22.1	22.7		
1962			19.2	6	23
1963	15		27.6		
1964			33.8		
1965		26.6 (est.)	32.3		
1966	26		38.0		
1967			43.0	22	41
1968	25				
1969					
1970					
1971				38	55
1972					
1973	46				

\* 1961-1968 data for females aged 20 years or older (176)  
 1973 data for females aged 17 years or older (177)

+ Females aged 21 years or older (178)

† Females aged 20 years or older (179)

Another means of assessing the extent to which cytology has been used is to determine the percentage of the adult female population that has had a Pap smear at any time in the past. Information of this nature has been collected by surveys encompassing the entire United States and by several smaller scale efforts involving only specific communities. Table 4 presents survey data for the United States and for three specific counties: Shelby County, Tennessee; Alameda County, California; and San Diego County, California. Corresponding data for British Columbia are included. The British Columbia information was not obtained by survey but by calculations involving population vital statistics, migration, and screening data.

Upon inspection of these data, it is apparent that the growth of cervical cytology screening has been regular, although perhaps slower than some would have expected. Except for specific geographic areas where cervical cytology screening received attention early, a reasonably high level of utilization is only a recent development. (See Table 3.)

Has this time lag between the initial development of cervical cytology in the 1940s and its widespread use been longer than it should have been? Three specific comments are perhaps representative of current views:

Dr. Leopold Koss:

[T]his was done faster and probably better than the mass application of any new discovery. Don't forget that this was the first mass cancer prevention program in the history of mankind. Regardless of how imperfect it might be this is the first successful cancer prevention program ever. (180)

Dr. John Dunn:

It was a long time...[but you] will always have the same experience as long as you invade private practice procedure. Any time that private physicians feel that someone is invading their bailiwick they are going to be resistant. (181)

Dr. Shields Warren:

I'd say it's par for the course. (182)

Whether cervical cytology screening is reaching the population at highest risk is another concern. Table 4 indicates that the penetration has been less than complete. Generally, those in the low socioeconomic groups are at highest risk and it is those same individuals who traditionally have been the most difficult to reach for participation in screening. Thus, for cervical cancer to be effectively eliminated, it will be necessary to concentrate on bringing these hard-to-reach, high-risk groups into screening. Evidence suggests that this is now being achieved in some areas of the United States.

Table 5 presents data showing the improvement in the level of cytologic screening by demographic variables in Alameda County, California from 1962 to 1974. Similar U.S. data for 1973 is presented in Table 6. Both tables suggest that it is those with a lesser amount of education and the elderly who are not being reached with screening. The lower portion of Table 6 suggests that this represents to a large extent a single cohort that is both old and without extensive education.



Table 4: Population Cytologic Survey Data: Penetration of Screening

Year	Percent of Adult Female Population Having Had One or More Examinations				British # Columbia
	U.S. *	Shelby + County Tennessee	Alameda + County California	San Diego # County California	
1961	30			62 (city only)	24
1962			51	72 (county exclusive of city)	
1963	38; 48	83 white 69 nonwhite			42
1965					55
1966				82	
1967					65
1969					73
1970	53				
1971					81
1973	75				85
1974			91		

\* 1961 figure and high 1963 figure based on Gallup survey data (183); low 1963 figure from University of Michigan survey data (184); 1970 figure from Gallup survey data (185); 1973 figure from National Center for Health Statistics data (186)

+ Kashgarian, M., Erickson, C.C., Dunn, J.E., et al (187)

‡ Unpublished data from Cal. State Health Dept., Human Population Lab. and Breslow, L. and Hochstim, J.R. (188)

# Papanicolaou Smear Survey (189)

‡ Unpublished data from Cancer Control Agency of British Columbia-Cytology Laboratory (data not obtained by population survey)

Table 5: Comparison of Pap Test Data  
from 1962 Survey and 1974 Survey:  
Alameda County, California

	1962 Survey (N-946)	1974 Survey (N-1710)
<u>Heard of Pap Test</u>	<u>Percent</u>	<u>Percent</u>
Yes	80	97
No	20	3
<u>Ever Had Pap Test</u>		
Yes	51	91
No	} 49	6
Don't Know		4
<u>Ever Had Pap Test</u>	<u>Percent "Yes"</u>	<u>Percent "Yes"</u>
Age Group:		
16 - 29	35	93
30 - 44	60	95
45 - 64	58	93
65 & over	36	74
Ethnic Group:		
Native white	57	93
Black	33	90
Oriental	26	68
Other	--	89
Foreign born white	33	85
Educational Level:		
0 - 8 years	39	76
9 - 12 years	51	92
13 or more years	60	93

Source: Unpublished data, California State Department of Health,  
Human Population Laboratory

Table 6: Characteristics of U.S. Females in 1973 Having a Pap Smear

	<u>At Least One Pap Smear Within Year</u>	<u>At Least One Pap Smear Within 4 years</u>	<u>Ever Had Pap Smear</u>
All Females 17 years and over	45.8	73.5	75.2
17 - 24 years	50.1	61.3	61.4
25 - 44 years	60.0	86.2	90.0
45 - 64 years	39.3	67.1	78.9
65 years and over	22.0	42.3	53.7
White	46.0	69.0	76.0
Nonwhite	44.8	65.4	69.4
Less than 12 years education	33.3	56.3	65.2
12 years education	51.6	75.7	81.4
13 years or more education	58.5	79.1	83.5
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All Females with less than 12 years education	33.3	56.3	65.2
17 - 24 years	38.6	49.6	49.6
25 - 44 years	49.2	77.7	83.9
45 - 64 years	31.3	58.9	71.8
65 years and over	19.0	38.3	49.7

Source: Adapted from National Center for Health Statistics data. (190)

Table 7 presents data on the incidence of invasive cervical cancer as determined by the Second and Third National Cancer Surveys. There has been a very notable and uniform drop in incidence over the 20-year period for all females beginning with the 30 to 34 age group. Data from other sources support this general trend. (191) Although the drop in incidence coincides with a general increase in intensity and penetration of screening, without additional and more detailed data on both incidence and screening, it is not possible to draw any firm conclusions regarding the contribution of screening to this trend.

Table 7: Annual Incidence Rates for Invasive  
Cervical Cancer from National Surveys

Age Groups	<u>All Females</u>		<u>White</u>		<u>Nonwhite</u>	
	<u>1947</u>	<u>1969-70</u>	<u>1947</u>	<u>1969-70</u>	<u>1947</u>	<u>1969-70</u>
< 5	0.9	0.1	1.0	0.1	0.0	0.0
5 - 9	0.0	0.0	0.0	0.0	0.0	0.0
10 - 14	0.4	0.1	0.5	0.1	0.0	0.0
15 - 19	1.2	0.6	0.9	0.5	2.5	0.4
20 - 24	2.5	3.2	1.8	2.4	6.2	7.4
25 - 29	8.9	13.8	5.7	12.0	26.4	23.7
30 - 34	31.8	19.3	27.9	16.2	54.4	36.4
35 - 39	49.5	26.9	41.0	23.1	95.8	45.4
40 - 44	77.5	32.6	71.3	26.9	117.3	67.5
45 - 49	97.3	35.1	84.2	32.6	184.9	48.8
50 - 54	113.2	32.0	107.1	27.4	165.2	61.3
55 - 59	116.6	38.2	113.0	32.7	157.7	77.5
60 - 64	105.3	38.7	95.2	32.2	229.9	85.1
65 - 69	105.6	43.5	92.3	36.7	235.4	91.0
70 - 74	93.7	39.3	88.4	35.6	165.7	73.6
74+	94.7	43.2	90.5	36.9	154.6	108.2

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Source: Cramer, D.W. (192)



In specified geographic areas where aggressive screening programs have been in effect, the observed rise and then drop in invasive cancer incidence has been attributed to screening. (193) In a recent review of the impact of screening on incidence of invasive cancer of the cervix in the Canadian provinces, it was concluded that only in Saskatchewan could it be reliably stated that screening affected incidence. (194) In two provinces incidence was declining before the onset of screening, and in the other two the absence of prescreening data precluded statements supporting the favorable impact of screening.

What effect has the increase in the use of cervical cytology had on mortality to date? As evident from Figure 1, the decline in uterine cancer mortality began before the development of cervical cytology. Several factors have been identified as possibly contributing to this early decline. Historically, an increasing percentage of women have been receiving hysterectomies, (195) and in the early 1940s gynecologists started performing total hysterectomies instead of so-called sub-total hysterectomies in which the cervix was not removed. (196) By 1973, the rate of hysterectomies in the female population had risen to 647.7 per 100,000 women. This represents 8.6 percent of the female population age 15 and older, a rate which if continued in the future will result in more than half the female population losing their uterus by the age of 65 years. (197)

A more significant factor influencing the pre-Pap test decline in uterine cancer mortality may have been the dramatically changing social scene. According to Dr. Koss:

It is also very possible that in the '30s and '40s we began to reduce to some extent the prime target population of cervix cancer--poverty and ignorance. I think it has something to do with the social movement--the way we were just emerging from the Great Depression. (198)

Dr. Wood has offered improvement in hygiene as a specific social factor:

I think part of this may be improvement in hygiene.... People just didn't clean themselves. They didn't bathe, they didn't do all sort of things....I don't think it is due to the fact that there has been a change in the carcinogens...they're just cleaner...hygiene may have a lot to do with this. (199)

Looking more closely at time trends for those deaths attributed to just cancer of the cervix (Figure 1) reveals support for the role of cytology in the reduction of mortality; the downward trend has begun to accelerate in recent years. It is not reasonable to expect an impact on cervix cancer mortality until at least 10 years after cytology is first widely applied. Thus, as can be seen from Figure 2, there has not yet been a sufficient passage of time for the complete effect on U.S. mortality to become manifest.

But in select subpopulations, such as those which were the specific targets of early screening programs, a high level of participation was reached much earlier. Here, where extensive early screening took place, the data indicate that cytologic screening is correlated with a significant reduction of cancer mortality. (200,201,202)

The extent to which this favorable trend can be attributed to cervical cancer screening is still questioned by some, (203) but general acceptance appears to be growing. (204,205) For example, after evaluating the effectiveness of screening for cancer of the cervix, the Committee on Cancer Prevention and Detection of the International Union Against Cancer concluded that the use of cytology as a population screening procedure promises useful yields

of preinvasive or early cancer and potential reduction in mortality. (206)  
Recent reviews, which address specifically the question of whether the  
evidence supports cervical cytology as providing a significant con-  
tribution to the reduction in cervical cancer mortality, provide per-  
suasive evidence that cytologic screening is indeed effective in reducing  
the death rate. (207,208)

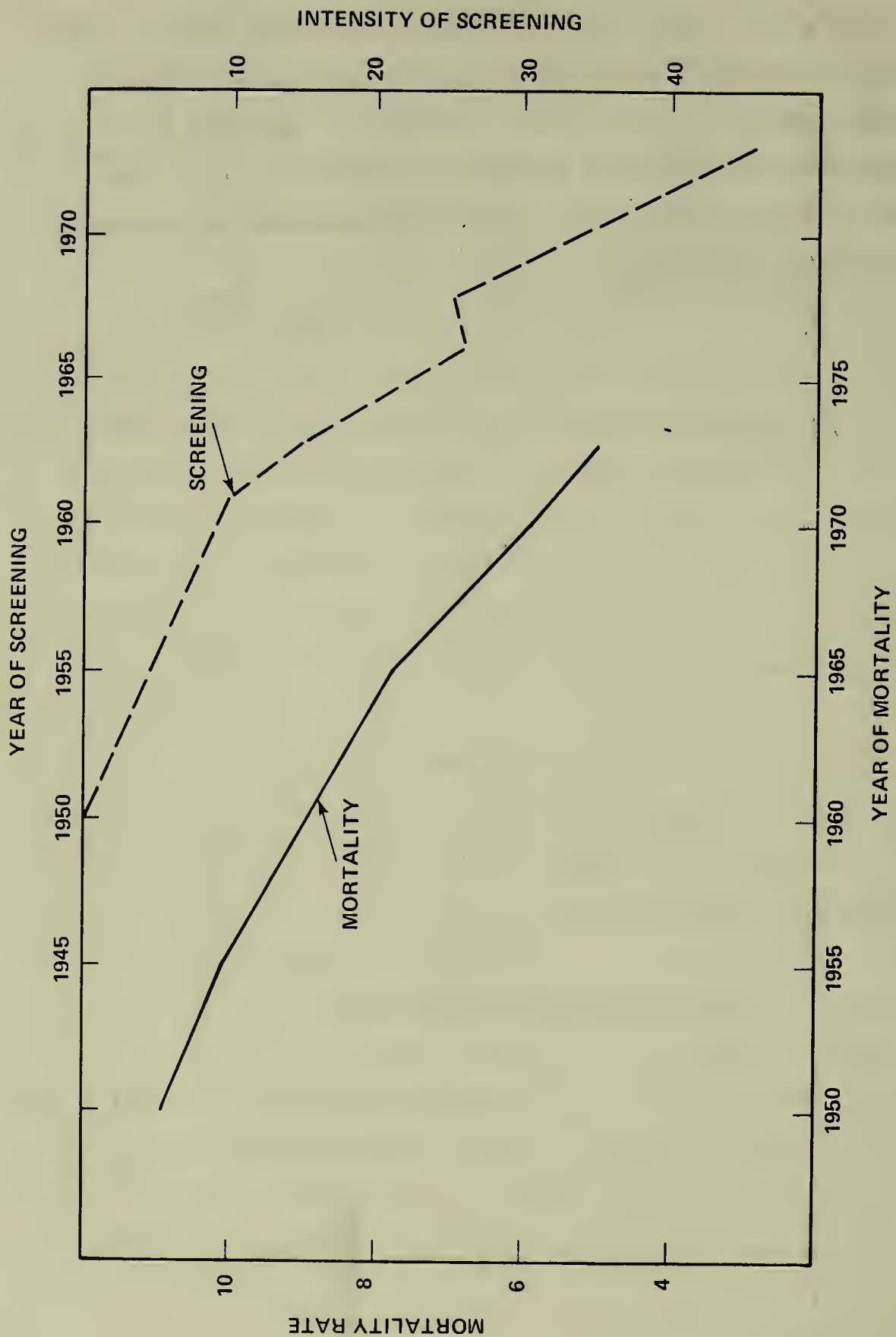


Figure 2: Age-Adjusted Mortality from Cervix Cancer in Relation to Screening



## Reflections on the Pace of Progress

In reflecting upon the history of cervical cytology, its course appears to have included three phases: development of the technology; the establishment of its role; and its mass application.

In summarizing the factors which were important in the developmental phase of cervical cytology, three appear noteworthy (beyond serendipity).

. Dr. Papanicolaou's attention to detail and devotion to his work were responsible for his developing the research base from which cytology could be developed into a practical clinical methodology.

. However, Dr. Papanicolaou's inclination to work on problems which were "in favor" at the time kept him from pursuing his early promising results in cervical cytology.

. Significant progress and credibility were achieved when a gynecologist (active in the care of patients) collaborated with Dr. Papanicolaou. The method was shown to have practical merit for the practicing physician.

The decade following the development of the Pap smear technique was one of professional adaptation. Out of this came new cytologic societies and at least one journal devoted to gynecologic cytology. Several factors were significant during this period of adjustment.

. The caution on the part of pathologists to endorse cytology as a complement to diagnosis based on tissue examination slowed the development of the knowledge base necessary to optimize the application of cytology in detection. The concept of diagnosis based on examination of cells rather than tissue was considered by most too much of a departure to appear practical.

. The American Cancer Society played an early and important role in furthering the application of cervical cytology. The method, after it was shown to be technically promising, was attractive to the ACS because of

its potential as a cancer control measure suitable for the general population. However, ACS program policy was dictated not by the lay public but by the elite of American medicine. The American Cancer Society moved conservatively when encouraged to do so by special interest groups within the medical community.

. Recognition and demonstration by the NCI that the method could be carried out by nurses and trained technicians (without the involvement of physicians) was beneficial, but it may have slowed acceptance. Elements within the medical community saw a potential threat to their traditional role with patients.

As cervical cytology was progressing into the phase of mass application, several forces were involved.

. While the federal Cancer Control Program was supportive and helped to advance cytology, particularly by furthering training, the momentum of its efforts was tempered by the multiple organizational relocations that Cancer Control experienced within the federal government. Furthermore, the general medical community did not want to see cancer control or any other part of medicine under the guidance of the federal government.

. Financial forces also were significantly involved. Cytology was viewed as a development with the potential for an unfavorable financial impact on various segments of medicine. It, therefore, encountered resistance. Pathologists were first resistant to cervical cytologic screening, while gynecologic clinicians saw it as a favorable development. However, as the method became accepted and cancer detection clinics were established, clinicians then too became concerned. "They were afraid that the whole movement would get into a big super clinic business." (209) It was this concern that actually stimulated the concept of every doctor's

office being a cancer detection center and the subsequent Office-Detected Cancer Program under joint sponsorship with organized medicine.

Cervical cytology is a screening methodology (one of few) that meets all the criteria necessary to ensure that the public will actually benefit from its application. Yet in spite of the general recognition of its value and the straightforwardness of its application, widespread utilization throughout the United States is still proceeding only on a gradual basis, with particular deficiencies noted in reaching high-risk segments of the population. In addition, it must be recognized that mass screening is only one in a series of steps in the control of uterine cancer, and without follow-up of positives, including effective treatment, nothing will have been accomplished.

Dr. John Dunn has succinctly asserted the lesson--and the challenge to cancer control--posed by the history of cytologic screening for cervical cancer: "If we can't make this work, we can forget about everything else." (210)

Chronology of Significant Events  
Influencing the Control of Cervical Cancer

- 1847 Pouchet recorded early observations on exfoliative cytology of the female genital tract. (Investigations were directed toward unstained normal cells of the vagina and their relation to ovulation, menstruation and conception).
- 1886 Original description of atypical epithelium by Williams.
- 1895 Ries developed an operative technique by working on dogs and cadavers that was essentially the technique that was later to be known as the Wertheim hysterectomy. (211) This technique was first used on patients beginning in 1895 by at least three surgeons).
- 1898 Wertheim started the series of radical hysterectomies that was to bear his name. (212)
- 1905 Wertheim's results demonstrated a significant improvement in patient management over the previous century. He reported an operability rate of 50 percent with an operative mortality of 20 percent. (213)
- 1908 Schauenstein introduced the idea that carcinoma of the cervix originated from abnormal epithelium.
- 1910 Rubin stressed the significance of a lesion of the cervix which had all the features of cancer except that it was non-invasive. The term carcinoma in-situ was given to this lesion in 1932 by Broders. (214)
- 1912 Schottlaender and Kermauner drew attention to the importance of the presence of superficial neoplastic epithelium located adjacent to invasive cancer of the cervix--the Schottlaender-Kermauner phenomenon.
- 1915 Bailey and Quimby devised a method to irradiate cervical cancer and its routes of dissemination. (215)
- 1924 Hinselmann invented the colposcope.
- 1928 Babes reported on a smear method of cervical cancer diagnosis.
- 1928 Development of Schiller test for diagnosis of cervical cancer.
- 1928 Concept of cytologic screening for cancer introduced by Papanicolaou.
- 1933 Report by Papanicolaou on the normal exfoliative cytology of the human vagina and its cyclic manifestations contained small paragraphs on malignant cytology.



- 1941 Paper by Papanicolaou and Traut on diagnostic value of vaginal smears in carcinoma of the uterus. Epic monograph was published in 1943.
- 1943 to 1946 Independent confirmation of Papanicolaou and Traut's work was developed by other investigators.
- 1947 Ayre introduced a direct cervical scrape method which generally displaced the original Papanicolaou method of using a rubber bulb to aspirate vaginal fluid.
- 1947 and 1948 The first reports emerged on the use of cervical cytology to detect symptomless carcinoma.
- 1948 The first National Conference on Cytology (sponsored by the ACS) was held in Boston.
- 1948 The first two schools for cytology training were established at Cornell (Papanicolaou) and the University of California at San Francisco (Traut).
- 1949 Antoine and Grunberger introduced the colpomicroscope.
- Late 1940s Large-scale organized population screening programs were initiated.
- Late 1940s and early 1950s Resistance of pathologists emerged to the expansion of cervical cytology without first establishing adequate standards and certification to ensure quality control.
- 1952 Hertig and Younger reviewed the significance of carcinoma in-situ as preinvasive stage of carcinoma.
- 1952 NCI established a large-scale cytology program for screening general population in Shelby County, Tennessee.
- 1952 The Inter-Society Cytology Council was established to bring clinicians and pathologists together on a national level to foster widespread application of cervical cytology.
- 1950s Cytologic screening units were established throughout the U.S.
- Middle and late 1950s Development and testing of methods of self-obtained tampon smears were initiated.
- 1956 NCI established and supported a large-scale screening program in Louisville to demonstrate the impact of screening on cervical cancer mortality.

- 1956 The first International Cancer Congress was held.
- 1957 The International Academy of Gynecological Cytology and the periodical Acta Cytologica were founded.
- 1958 Uterine Cancer Year was proclaimed by the American Cancer Society.
- Late 1950s NCI began support of research on automation of cytologic slide interpretation.
- Early & middle 1960s Development and testing of self-obtained vaginal irrigation smears proceeded.
- Middle 1960s NCI and the American Academy of General Practice initiated the Office-Detected Cervical Cancer Program.
- Late 1960s & early 1970s Numerous reports emerged dealing with the evaluation of the impact of mass cytologic screening on cervical cancer incidence and mortality.
- 1972 UICC Committee on Cancer Prevention and Detection concluded that the use of cytology on a population screening procedure promises useful yields of early cancer and potential reduction in mortality.

- (1) Ewing, J.: The prevention of cancer. In Cancer Control. Report of an International Symposium held under the auspices of the American Society for the Control of Cancer, Lake Mohonk, New York, September 20-24, 1926, pp. 165-169, at 169.
- (2) Cameron, C.S.: Cancer of the uterus: problem, progress and promise. In Proceedings of World Conference on Cancer of the Uterus. American Cancer Society, 1969, at 9-16.
- (3) See note (2) at 9.
- (4) Cutler, S.J., Myers, M.H., Green, S.B.: Trends in survival rates of patients with cancer. New Eng. J. Med. 293:122-124, 1975.
- (5) Christopherson, W.M., Parker, J.E.: Relation of cervical cancer to early marriage and childbearing. New Eng. J. Med. 273:235-239, 1965.
- (6) Hammond, E.C.: The Walter I. Hubert Lecture: The early diagnosis of uterine cancer. In Riggott, J.M. (ed.): The Early Diagnosis of Cancer of the Cervix. University of Hull, 1971.
- (7) See note (1) at 169.
- (8) Williams, J.: Cancer of the Uterus, Harveian Lectures for 1886. London, H.K. Lewis, 1888. As referenced in Friedell, G.H., Hertig, A.T., Younge, P.A.: Carcinoma in Situ of the Uterine Cervix. Springfield, Charles C. Thomas, 1960, at 5.
- (9) Schauenstein, W.: Histologische Untersuchung über atypisches Plattenepithels an der Portio und an der Innenfläche der Cervix uteri. Arch. Gynäk. 85:576-616, 1908.
- (10) Pronai, K.: Zur Lehre von der Histogenese an dem Wachsthum des Uteruscarcinoms. Arch. Gynäk. 89:596-607, 1909.
- (11) Rubin, I.C.: The pathological diagnosis of incipient carcinoma of the uterus. Am. J. Obstet. 62:668-676, 1910.
- (12) Schottlaender, J., Kermauner, F.: Zur Kenntnis des Uteruskarzinoms. Berlin, Verlag von S. Karger, 1912.
- (13) See note (9).
- (14) See note (11).
- (15) See note (12).

- (16) Interview with Dr. Leopold Koss, Chairman of the Department of Pathology, Albert Einstein College of Medicine, by Leon Ellwein of HCCP, March 5, 1976, New York City, N.Y.
- (17) Hinselmann, H.: Verbesserung der Inspektionsmöglichkeiten von Vulva, Vagina und Portio. Munch. Med. Wschr. 72:1733, 1925.
- (18) Antoine, T., Grunberger, V.: Die Auflichtmikroskopie in der Gynäkologie. Klin. Med. 4:575-579, 1949.
- (19) Coppleson, M., Reid, B., Pixley, E.: Preclinical Carcinoma of the Cervix Uteri. Oxford, Pergamon Press, 1967, at 16.
- (20) See note (16).
- (21) Nelson, J.H., Averette, H.E., Richart, R.M.: Detection, diagnostic evaluation and treatment of dysplasia and early carcinoma of the cervix. CA 25:134-151, 1975.
- (22) Schiller, W.: Early diagnosis of carcinoma of the cervix. Surg., Gynec. & Obstet. 56:210-222, 1933.
- (23) Pouchet, F.A.: Theorie positive de l'ovulation spontanee et de la fecondation des mammiferes et de l'espece humaine, basee sur l'observation de toute la serie animale; avec atlas. Paris, J. B. Bailliere, 1847, at 479.
- (24) Naylor, B.: The history of exfoliative cancer cytology. Univ. Mich. Med. Bull. 26:289-296, 1960.
- (25) Douglass, L.: A further comment on the contributions of Aurel Babes to cytology and pathology. Acta Cytol. 11:217-224, 1967.
- (26) Babes, A.: Diagnostic du Cancer du Col Uterin par les Frottis. La Presse Medicale 36:451-454, April 11, 1928.
- (27) See note (26).
- (28) See note (25).
- (29) Douglass, L.: Odorico Viana and his contribution to diagnostic cytology. Acta Cytol. 14:544-549, 1970.
- (30) Viana, O.: La diagnosi precoce del cancro uterino mediante lo striscio. La Clinica Ostetrica 30:781-793, 1928.
- (31) Papanicolaou, G.N.: New cancer Diagnosis. In Proceedings of the Third Race Betterment Conference. Race Betterment Foundation, Battle Creek, Michigan, 1928, pp. 528-534.
- (32) Koss, L.G.: George N. Papanicolaou. Presidential address delivered at The 10th Annual Meeting of American Society of Cytology. Acta Cytol. 7:143, 1963.



- (33) Carmichael, D.E.: The Pap Smear: Life of George N. Papanicolaou. Springfield, Charles C. Thomas, 1973.
- (34) See note (31).
- (35) See note (16).
- (36) See note (31).
- (37) See note (33).
- (38) Papanicolaou, G.N.: Historical development of cytology as a tool in clinical medicine and in cancer research. Int. Union Cancer, Acta 14:249-254, 1958, at 252.
- (39) Papanicolaou, G.N.: The evolutionary dynamics and trends of exfoliative cytology. Tex. Rep. Biol. Med. 13:901-919, 1955, at 906-907.
- (40) See note (38) at 252.
- (41) See note (33).
- (42) Papanicolaou, G.N.: The sexual cycle in the human female as revealed by vaginal smears. Am. J. Anat. (Supp.) 52:519-637, 1933, at 534.
- (43) See note (24) at 292.
- (44) Hinsey, J.C.: George Nicholas Papanicolaou. Acta Cytol. 6:483-486, 1962, at 484-485.
- (45) Interview with Dr. David Wood, Cancer Research Institute, University of California, San Francisco, by Devra Breslow and Leon Ellwein of HCCP, October 11, 1976, San Francisco, Ca.
- (46) Interview with Dr. John Dunn, California State Department of Public Health, by Devra Breslow of HCCP, April 1, 1976, Berkeley, Ca.
- (47) Interview with Dr. Charles Cameron, former Medical and Scientific Director of the American Cancer Society, by Devra Breslow of HCCP, May 22, 1976, Miami Beach, Fla.
- (48) Papanicolaou, G.N., Traut, H.F.: Diagnosis of Uterine Cancer by the Vaginal Smear. New York, The Commonwealth Fund, 1943.
- (49) Papanicolaou, G.N., Traut, H.F.: The diagnostic value of vaginal smears in carcinoma of the uterus. Am. J. Obstet. Gynec. 42:193-206, 1941.
- (50) Meigs, J.V., Graham, R.M., Fremont-Smith, M., et al: The value of the vaginal smear in the diagnosis of uterine cancer. Surg., Gynec. & Obstet. 77:449-461, 1943.

- (51) Jones, C.A., Neustaedter, T., MacKenzie, L.L.: The value of vaginal smears in the diagnosis of early malignancy. Am. J. Obstet. Gynec. 49:159-168, 1945.
- (52) Ayre, J.E.: A simple office test for uterine cancer diagnosis. Canad. Med. Assoc. J. 51:17-22, 1944.
- (53) Meigs, J.V., Graham, R.M., Fremont-Smith, M., et al: The value of the vaginal smear in the diagnosis of uterine cancer. Surg., Gynec., & Obstet. 81:337-345, 1945.
- (54) Ayre, J.E.: Vaginal and cervical cytology in uterine cancer diagnosis. Am. J. Obstet. Gynec. 51:743-748, 1946.
- (55) Ruth Moore Graham. Acta Cytol. 2:6-10, 1958, at 6-7.
- (56) See note (45).
- (57) Hinsey, J.C.: George Nicholas Papanicolaou. Acta Cytol. 6:483-486, 1962.
- (58) See note (16).
- (59) Interview with Dr. J. R. Heller, former Director, National Cancer Institute, by Devra Breslow of HCCP, November 4, 1975, Bethesda, Md.
- (60) See note (47).
- (61) Ikeda, K.: The Papanicolaou method of cancer diagnosis: an evaluation. Minn. Med. 32:54-56, 64, 93, 1949, at 54.
- (62) See note (45).
- (63) Lapid, L.S., Klemperer, P.: Teamwork between pathologists and cytologists. Ann. N.Y. Acad. Sci. 63:1066-1069, 1956, at 1066-1067.
- (64) See note (63) at 1066.
- (65) Pund, E.R., Nieburgs, H.E., Nettles, J.B., et al: Preinvasive carcinoma of the cervix uteri. Arch. Path. 44:571-577, 1947.
- (66) Nelson, R.B., Hilberg, A.W.: The diagnosis of unsuspected cancer of the cervix. J. Nat. Cancer Inst. 11:1081-1089, 1951.
- (67) Lombard, H.L., Middleton, M., Warren, S., et al: Use of the vaginal smear as a screening test. New Eng. J. Med. 239:317-321, 1948.
- (68) McSweeney, D.J., McKay, D.G.: Uterine cancer: its early detection by simple screening methods. New Eng. J. Med. 238:867-870, 1948.
- (69) L'Esperance, E.S.: The early diagnosis of cancer. Bull. N.Y. Acad. Med. 23:394-409, 1947.

- (70) Kernodde, J.R., Cuyler, K., Thomas, W.L.: The diagnosis of genital malignancy by vaginal smears. Am. J. Obstet. Gynec. 56:1083-1089, 1948.
- (71) See note (67).
- (72) See note (67) at 317-318.
- (73) Interview with Dr. Shields Warren of the Cancer Research Center, New England Deaconess Hospital, by Devra Breslow of HCCP, June 15, 1976, Boston, Mass.
- (74) See note (67) at 317.
- (75) See note (67) at 317.
- (76) Younge, P.A.: The early diagnosis and treatment of early cancer of the cervix. N.Y. State J. Med. 50:2519-2524, 1950, at 2519.
- (77) Pund, E.R., Auerbach, S.H.: Preinvasive carcinoma of the cervix uteri. J.A.M.A. 131:960-963, 1946.
- (78) See note (76) at 2519.
- (79) See note (70) at 1088.
- (80) Burns, E.L., Gorski, T.W.: The application of cytology to a community uterine cancer detection program. Am. J. Obstet. Gynec. 77:973-976, 1959.
- (81) See note (80).
- (82) Burns, E.L., Hammond, E.C., Percy, C., et al: Detection of uterine cancer. Results of a community program of 17 years. Cancer 22:1108-1119, 1968.
- (83) Martin, P.L., Slate, T.A., Merritt, J.W.: Routine smears--a practical method for cytodetection of unsuspected cervical cancer. West. J. Surg. 61:102-105, 1953.
- (84) See note (46).
- (85) Boyes, D.A., Fidler, H.K., Lock, D.R.: Significance of in situ carcinoma of the uterine cervix. Brit. Med. J. 1:203-205, 1962.
- (86) See note (38) at 252.
- (87) See note (47).
- (88) See note (45).

- (89) Meigs, J.V.: The history of the Inter-Society Cytology Council. Ann. N.Y. Acad. Sci. 63:1041-1045, 1956.
- (90) See note (89) at 1041.
- (91) Fletcher, P.F.: The Inter-Society Cytology Council Progress Report. In Proceedings of the Second National Cancer Conference. New York, American Cancer Society, 1952, pp. 1182-1189.
- (92) See note (91) at 1183.
- (93) See note (91) at 1184-1185.
- (94) Day, E.: Accomplishments and shortcomings of cancer cytology. Ann. N.Y. Acad. Sci. 63:1070-1077, 1956, at 1070.
- (95) See note (94) at 1076.
- (96) King, J.F.W.: The Uterine-Cytology Program of the American Cancer Society. CA 7:136-137, 1957.
- (97) See note (96) at 136.
- (98) See note (38) at 253.
- (99) Papanicolaou, G.N.: Cytologic diagnosis of uterine cancer by examination of vaginal and uterine secretions. Am. J. Clin. Path. 19:301-308, 1949.
- (100) See note (47).
- (101) See note (66).
- (102) Kaiser, R.F., Erickson, C.C., Everett, B.E., et al: Initial effect of community-wide cytologic screening on clinical stage of cervical cancer detected in an entire community. Results of Memphis-Shelby County, Tennessee study. J. Nat. Cancer Inst. 25:863-881, 1960.
- (103) Erickson, C.C., Everett, Jr., B.E., Graves, L.M., et al: Population screening for uterine cancer by vaginal cytology. J.A.M.A. 162:167-173, 1956.
- (104) Dunn, J.E., Sprunt, D.H.: Uterine cancer case finding by vaginal cytology. Pub. Health Rep. 70:341-346, 1955.
- (105) Erickson, C.C.: Early uterine cancer detection by cytologic screening, Ann. N.Y. Acad. Sci. 63:1054-1065, 1956.
- (106) Dunn, J.: Proposed Cytologic Study of the Adult Female Population of Memphis and Shelby County, Tennessee for Genital Tract Cancer Case Finding. Unpublished proposal prepared for presentation to the National Cancer Advisory Council, 1950.



- (107) See note (46).
- (108) See note (106) at 1-2.
- (109) See note (46).
- (110) Interview with Dr. Lewis Robbins, former Chief, Cancer Control Program, NCI, by Lester and Devra Breslow of HCCP, November 20, 1975, Indianapolis, Ind.
- (111) Hertig, A.T., Young, P.A.: A debate--what is cancer in situ of the cervix? Is it a preinvasive form of true carcinoma? Am. J. Obstet. Gynec. 64:807-815, 1952.
- (112) See note (111) at 815.
- (113) McKelvey, J.L.: Carcinoma in situ of the cervix: A general consideration. Am. J. Obstet. Gynec. 64:816-832, 1952, at 830.
- (114) See note (104).
- (115) See note (46).
- (116) See note (104).
- (117) Interview with Dr. Raymond Kaiser, former Chief, Cancer Control Program, NCI, by Devra Breslow of HCCP, April 27, 1976, San Francisco, Ca.
- (118) See note (117).
- (119) Christopherson, W.M., Mendez, W.M., Ahuja, E.M., et al: Cervix cancer control in Louisville, Kentucky. Cancer 26:29-38, 1970, at 29.
- (120) Christopherson, W.M., Parker, J.E., Drye, J.C.: Control of cervical cancer--preliminary report on community program. J.A.M.A. 182:179-182, 1962, at 179.
- (121) Christopherson, W.M., Parker, J.E., Mendez, W.M., et al: Cervix cancer death rates and mass cytologic screening. Cancer 26:808-811, 1970.
- (122) Christopherson, W.M., Parker, J.E.: Control of cervix cancer in women of low income in a community. Cancer 24:64-69, 1969.
- (123) Christopherson, W.M., Mendez, W.M., Ahuja, E.M., et al: Cervix cancer control in Louisville, Kentucky. Cancer 26:29-38, 1970.
- (124) See note (121).
- (125) Staff of the National Cancer Institute. J. Nat. Cancer Inst. 19:339-348, 1957.

- (126) Kaiser, R.F., Bouser, M.M., Ingraham, S.C., et al: Uterine cytology. Pub. Health Rep. 75:423-427, 1960.
- (127) Calabresi, P., Arvold, N.V., Stovall, W.D.: Cytological screening for uterine cancer through physicians' offices: report of 65,163 women examined over a period of ten years (1947-1956). J.A.M.A. 168:243-247, 1958.
- (128) See note (82).
- (129) Quisenberry, W.B.: Exfoliative cytology laboratory service in a community cancer control program. Postgrad. Med. 34:559-563, 1963.
- (130) Dunn, Jr., J.E., Slate, T.A., Merritt, J.W., et al: Findings for uterine cancer from one or more cytologic examinations of 33,750 women. J. Nat. Cancer Inst. 23:507-527, 1959.
- (131) Nieburgs, H.E., Stergus, I., Stephenson, E.M., et al: Mass screening of the total female population of a county for cervical carcinoma. J.A.M.A. 164:1546-1551, 1957.
- (132) Kimmelstiel, P., Bos, J.F., Nolen, C.: Community survey for uterine cancer. Obstet. Gynec. 11:688-695, 1958.
- (133) See note (102).
- (134) Stern, E.: Rate, stage, and patient age in cervical cancer. An analysis of age specific discovery rates for atypical hyperplasia, in situ cancer, and invasive cancer in a well population. Cancer 12:933-937, 1959.
- (135) Miller, E.M., von Haam, E.: A comparison of the vaginal aspiration and cervical scraping technics in the screening process for uterine cancer. Acta Cytol. 5:214-216, 1961.
- (136) See note (122).
- (137) Bibbo, M., Keebler, C.M., Weid, G.L.: Prevalence and incidence rates of cervical atypia. A computerized file analysis on 148,735 patients. J. Reprod. Med. 6:79-83, 1971.
- (138) Figge, D.C., Bennington, J.L., Schweid, A.I.: Cervical cancer after initial negative and atypical vaginal cytology. Am. J. Obst. Gynec. 108:422-428, 1970.
- (139) Davis, H.J., Jones, H.W.: Population screening for cancer of the cervix with irrigation smears. Am. J. Obstet. Gynec. 96:605-618, 1966.
- (140) Kessler, I.I., Aurelian, L.: Uterine Cervix. In Schottenfeld, D. (ed.): Cancer Epidemiology and Prevention. Springfield, Charles C. Thomas, 1975, pp. 263-317, at 284.

- (141) See note (110).
- (142) See note (99).
- (143) Ayre, J.E.: Selective cytology smear for diagnosis of cancer. Am. J. Obstet. Gynec. 53:609-617, 1947.
- (144) Ayre, J.E.: Early cancer detection: Prediction of preclinical and preinvasive stages by cytology. Int. Union Cancer, Acta 15:284-295, 1959.
- (145) Berg, J.W., Bader, G.M.: The present potential of exfoliative cytology in the detection of cervix cancer. Cancer 11:758-764, 1958.
- (146) Close-Up. Routine gynecologic examination and cytologic smear. CA 25:281-285, 1975, at 283.
- (147) See note (48).
- (148) Gates, O., Warren, S.: The vaginal smear in diagnosis of carcinoma of the uterus. Am. J. Path. 21:567-601, 1945, at 567.
- (149) Brunschwig, A.: A method for mass screening for cytological detection of carcinoma of the cervix uteri. Cancer 7:1182-1184, 1954, at 1182.
- (150) Papanicolaou, G.N.: Cytological evaluation of smears prepared by the tampon method for the detection of carcinoma of the uterine cervix. Cancer 7:1185-1190, 1954, at 1190.
- (151) Bader, G.M., Simon, T.R., Koss, L.G., et al: A study of the detection-tampon method as a screening device for uterine cancer. Cancer 10:332-337, 1957.
- (152) Scott, R.B., Brown, A.M., Reagan, J.W.: Comparative results of the routine Papanicolaou and the Draghi tampon cytologic studies in atypical hyperplasia of the cervix and uterine cancer. Am. J. Obstet. Gynec. 73:349-353, 1957.
- (153) Davis, H.J.: The irrigation smear: A cytologic method for mass population screening by mail. Am. J. Obstet. Gynec. 84:1017-1023, 1962.
- (154) See note (139).
- (155) See note (139).
- (156) Ellesh, R.H., Hilker, R.J., Carrow, L.A.: The vaginal irrigation smear. Obstet. Gynec. 34:30-33, 1969.
- (157) Reagan, J.W., Lin, F.: An evaluation of the vaginal irrigation technique in the detection of uterine cancer. Acta Cytol. 11:374-382, 1967.

- (158) Anderson, W.A.D., Gumm, S.A.: Premalignant and malignant conditions of the cervix uteri--tissue validity study of the vaginal irrigation smear method. Cancer 20:1587-1593, 1967.
- (159) See note (16).
- (160) Courtney, W.B., et al: Field trial of the cytoanalyzer: 1,184 specimens analyzed. J. Nat. Cancer Inst. 24:1167-1179, 1960.
- (161) Tolles, W. E.: The cytoanalyzer--an example of physics in medical research. Trans. N.Y. Acad. Sci. 17:250-256, 1955.
- (162) Tolles, W.E., Bostrom, R.C.: Automatic screening of cytological smears for cancer: The instrumentation. Ann. N.Y. Acad. Sci. 63:1211-1218, 1956.
- (163) See note (160).
- (164) Spencer, C.C., Bostrom, R.C.: Performance of the cytoanalyzer in recent clinical trials. J. Nat. Cancer Inst. 29:267-276, 1962.
- (165) Nadel, E.M.: Computer analysis of cytophotometric fields by CYDAC and its historical evolution from the cytoanalyzer. Acta Cytol. 9:203-206, 1965.
- (166) See note (165).
- (167) Automated cytology. A symposium by correspondence. Acta Cytol. 15:1-24, 1971, at 3.
- (168) See note (167) at 8.
- (169) NIH Guide Supplement for Grants and Contracts. No. 10. Washington, D.C., DHEW, December 18, 1974.
- (170) Kashgarian, M., Dunn, J.E.: The duration of intraepithelial and preclinical squamous cell carcinoma of the uterine cervix. Am. J. Epidemiol. 92:211-222, 1970.
- (171) Cramer, D.W., Cutler, S.J.: Incidence and histopathology of malignancies of the female genital organs in the United States. Am. J. Obstet. Gynec. 118:443-460, 1974.
- (172) Axtell, L.M., Cutler, S.J., Myers, M.H.: End Results in Cancer, Report No. 4.
- (173) Horne, D., Siegel, A.: National survey of cytologic facilities: a special report. CA 11:97-100, 1961.
- (174) Manos, N.E., Robins, M.: Report on national surveys of cytologic facilities. CA 22:221-225, 1972.



- (175) National Center for Health Statistics. Characteristics of females ever having a Pap smear and interval since last Pap smear, United States, 1973. Monthly Vital Statistics Report, Vol. 24, No. 7 (Supp.). Washington, D.C., U.S. Govt. Printing Office, October 7, 1975.
- (176) See note (174) at 224.
- (177) See note (175).
- (178) Dickinson, L.M., Mussey, E., Kurland, L.T.: Evaluation of the effectiveness of cytologic screening for cervical cancer. I. Incidence and mortality trends in relation to screening. Mayo Clin. Proc. 47:534-544, 1972, at 537.
- (179) Cervical cancer screening programs: The Walton Report. Canad. Med. Assoc. J. 114:2-32, 1976, at 13.
- (180) See note (16).
- (181) See note (46).
- (182) See note (73).
- (183) Kashgarian, M., Erickson, C.C., Dunn, J.E., et al: A survey of public awareness of uterine cytology in Memphis-Shelby County. Acta Cytol. 10:11-14, 1966, at 11.
- (184) Kegeles, S.S., Kirscht, J.P., Haefner, D.F., et al: Survey of beliefs about cancer detection and taking Papanicolaou tests. Pub. Health Rep. 80:815-823, 1965, at 816.
- (185) Brown, A.J.: Awareness and use of cervical cancer tests in a Southern Appalachian community. Pub. Health Rep. 91:236-242, 1976, at 239.
- (186) See note (175) at 2.
- (187) See note (183) at 13.
- (188) Breslow, L., Hochstim, J.R.: Sociocultural aspects of cervical cytology in Alameda County, Calif. Pub. Health Rep. 79:107-112, 1964, at 110.
- (189) Papanicolaou Smear Survey - San Diego County. American Cancer Society, San Diego County Branch, June, 1967, at 37.
- (190) See note (175).
- (191) Cramer, D.W.: The role of cervical cytology in the declining morbidity and mortality of cervical cancer. Cancer 34:2018-2027, 1974.
- (192) See note (191) at 2022.

- (193) See note (123).
- (194) Cervical cancer screening programs: The Walton Report.  
Canad. Med. Assoc. J. 114:2-32, 1976.
- (195) See note (6).
- (196) See note (16).
- (197) Bunker, J.P.: Elective hysterectomy: pro and con.  
New Eng. J. Med. 295:264-268, 1976.
- (198) See note (16).
- (199) See note (45).
- (200) See note (121).
- (201) Dickinson, L.M., Mussey, E., Kurland, L.T.: Evaluation of the effectiveness of cytologic screening for cervical cancer. I. Incidence and mortality trends in relation to screening.  
Mayo Clin. Proc. 47:534-544, 1972.
- (202) Breslow, L.: Early case-finding, treatment, and mortality from cervix and breast cancer. Prev. Med. 1:141-152, 1972.
- (203) Kinlen, L.J., Doll, R.: Trends in mortality from cancer of the uterus in Canada and in England and Wales.  
Brit. J. Prev. Soc. Med. 27:146-149, 1973.
- (204) Boyes, D.A., Knowlenden, J., Phillips, A.J.: The evaluation of cancer control measures. Brit. J. Cancer 28:105-107, 1973.
- (205) Koss, L.G., Phillips, A.J.: Summary and recommendations of the Workshop on Uterine-Cervical Cancer. Cancer 33:1753-1754, 1974.
- (206) See note (204).
- (207) See note (191).
- (208) Miller, A.B., Lindsay, J., Hill, G.B.: Mortality from cancer of the uterus in Canada and its relationship to screening for cancer of the cervix. Int. J. Cancer 15:602-612, 1976.
- (209) See note (47).
- (210) See note (46).
- (211) Ries, E.: Eine neue Operationsmethode des Uteruscarcinoms.  
Zschr. Geburtsh. 32:266-274, 1895.
- (212) Wertheim, E.: Zur Frage der Radicaloperation beim Uteruskrebs.  
Arch. Gynäk. 61:627-668, 1900.

- (213) Wertheim, E.: A discussion on the diagnosis and treatment of cancer of the uterus. Brit. Med. J. 2:689-704, 1905.
- (214) Broders, A.C.: Carcinoma in situ contrasted with benign penetrating epithelium. J.A.M.A. 99:1670-1674, 1932.
- (215) Bailey, H., Quimby, E.H.: The use of radium in cancer of the female generative organs. Am. J. Obstet. Gynec. 3:117-133, 1922.





## CHAPTER 5

### THE ROLE OF MAMMOGRAPHY IN THE DETECTION OF BREAST CANCER

#### Introduction

Breast cancer will kill 33,000 women in the United States this year, and 88,000 new cases of this disease will be diagnosed. According to the American Cancer Society, the magnitude of the loss may be more comprehensible in the following terms:

- Every fifteen minutes three women will be diagnosed as having breast cancer; within each 15-minute period, a woman will be killed by the disease. (1)

- The total number of battle deaths in the Korean War is equal to the breast cancer mortality for one year in this country. (2)

- In the past ten years, the number of breast cancer deaths could have wiped out the entire population of Albuquerque, New Mexico. (3)

During the past 40 years, the incidence of breast cancer in women has actually increased by 10 percent, although the mortality rate from the disease has not changed during the same period. (4) (The gradual increase in the early diagnosis and survival rate of patients with breast

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cancer (5) may explain the stability of the mortality rate despite increased incidence.) At any one time 250,000 women in America may have breast cancer and be unaware of it, according to American Cancer Society statistics. (6)

In an effort to combat this problem, physicians have developed increasingly sophisticated modes of detecting breast cancer. Family history, clinical examination, and self-examination by the patient have been supplemented by technological advances. The most visible of these is mammography, which has made the idea of mass screening to detect non-palpable breast cancer a reality. (The concept of mass screening itself has generated its own controversy, as the conclusion of this chapter will discuss.) The current Breast Cancer Detection Demonstration Project, jointly sponsored by the National Cancer Institute and the American Cancer Society, is in the process of screening 270,000 women in 27 centers across the United States in an effort to reach women at a point early enough to prevent their deaths from the disease. But the history of mammography, which has made such screening projects feasible, has been evolutionary rather than revolutionary. From the time the first American study of breast radiography was published in 1930 by Dr. Stafford L. Warren, (7) 33 years elapsed before mammography was endorsed, in 1963, as a potentially valuable procedure by Dr. Luther L. Terry, Surgeon General of the United States. (8)

The factors that promoted and inhibited the development of mammography suggest lessons from which we may learn how the war against cancer may be waged more effectively in the future.

## Early Developments in Breast Radiology

After the invention of the "x-ray" was announced in January, 1896, several European researchers began to experiment with breast radiography. The first roentgen ray pictures of the breast were taken by Dr. Albert Salomon, who published his experiences in 1913 in Germany. (9) Salomon, a surgeon, did his work on 3,000 excised breasts in order to improve the quality of biopsy specimens. Perhaps because of World War I, Salomon never proceeded to the diagnostic application of his work, but his study was nevertheless the first recognition that a roentgenogram could clearly define a breast tumor and provided the first description of the radiographic differences between the most common forms of mammary cancer. (10,11)

After Salomon's paper appeared, nearly a decade passed before other European researchers began to investigate the value of roentgen diagnosis of breast lesions; none of their papers was published until the 1930s, however. In South America, Goyanes, Gentil, and Guedes studied the use of the roentgenogram as a diagnostic tool and advocated its further use by others. (12,13) During the same period (1924-30), physicians at a breast clinic in Leipzig were using roentgenograms for diagnostic purposes. While the supervisor of the clinic, Dr. Erwin Payr, made numerous contributions to research during his career, he never personally published his findings at the clinic. But two papers later emerged as products of the Leipzig experience. The first, by Vogel, (14) has been called a classic document (15) since its description of interpretive criteria is still valid today. Vogel accurately differentiated between the roentgenological appearances of benign and malignant lesions and included advice on roentgenographic technique. (16) The second paper, by Finsterbusch and Gross, (17) examined the calcifications characteristic

of secretory breast disease. The authors correlated roentgen and histologic pathology and attempted to biochemically analyze the lesions. (18)

During these years of research by a few physicians in Europe and South America, the American medical community was silent. The invention of the X-ray, the 1913 study of Salomon, and the work of the South American and German clinicians (which remained unpublished until the 1930s) failed to prompt interest in further roentgenographic investigation of breast disease in the United States. However, in 1926, while using the fluoroscope to obtain measurements of the thoracic aorta, Dr. Stafford L. Warren of Strong Memorial Hospital in Rochester, New York, made an interesting discovery: by moving back to a distance of six feet, he was able to obtain a roentgenogram of the breast. (19) Warren proceeded to study the pathological conditions in the breast by means of a stereoscopic technique and began to perform preoperative breast examinations at Strong Memorial Hospital. In August, 1930, his experiences were published in The American Journal of Roentgenology and Radium Therapy. (20) Among 119 patients whom Warren examined using his new technique and who were subsequently biopsied, 58 of the tissue specimens taken during operations or autopsies proved to be malignant. Warren had made an incorrect diagnosis in only 8 cases, missing 4 of the 58 malignancies and erroneously labeling "probably malignant" 4 cases that were later found to be among the 61 non-malignant specimens. Based on his study Warren concluded:

The diagnosis made from stereoscopic films of the breast corresponded very closely (85 to 95 percent) to the operative and autopsy findings. The results from the study of the breast roentgenograms seem to warrant the impression that this type of examination is of distinct clinical value. (21)



The 1930 article was the first recognition in America of the diagnostic potential of radiography in the study of breast disease. Nevertheless, Warren felt the publication earned neither support nor enthusiasm from his peers, who responded, if at all, with skepticism and apathy. (22) Dr. Michael B. Shimkin, Professor of Community Medicine and Oncology at the University of California at San Diego and former Associate Director for Field Studies at the National Cancer Institute, recalls that he had been "surprised by the low status accorded to breast cancer in the hierarchy of medical concerns" in the 1930s when he began his medical career. (23) In addition, Shimkin explained that radiologists at that time were quite skeptical about the quality of any soft tissue roentgenographic technique. (24) Looking back on the same era, Dr. Leo Rigler, international authority in the field of diagnostic radiology, agreed with the appraisal given by Shimkin. He also emphasized that surgeons of the early 20th century considered palpation to be an adequate mode of diagnosis and that a new roentgenographic diagnostic technique would thus hardly be hailed as a necessary or welcome innovation. (25)

Reflecting on his experience with the breast study, Warren remembers it as "a lonely business." (26) After his 1930 publication, he felt that he had accomplished his goal of describing how breast pathology changes during menstruation, pregnancy, lactation, and during various stages of malignant and non-malignant breast diseases, and he consequently returned to further studies of heart measurements. (27)

Warren's publication did succeed in generating an initial flurry of interest among some American researchers. In the early 1930s, studies

appeared by various investigators: Seabold (28,29,30) and Riemann and Seabold (31) published articles on roentgen changes in the breast, particularly during the normal menstrual cycle; Lockwood alone (32,33) and with Stewart (34) described additional diagnostic criteria. (Simultaneously with Warren's study and shortly thereafter, researchers in other countries had published their studies: Dominguez of Uruguay (35) and Baraldi of Brazil (36) reported on the use of pneumomammography, later adopted by Hicken in the U.S.; (37) Espaillet of France published an ambitious diagnostic manual in 1933, (38) and Gunsett and Sichel of France formulated further diagnostic criteria in 1934. (39))

However, the initial interest created by Warren's study subsided. Those who have chronicled the history of mammography (40) have speculated that there may have been several reasons for the short-lived nature of the enthusiasm. Primarily, it is felt that later researchers may have become discouraged when they were unable to reproduce Warren's results with the same high degree of accuracy; this may have been due to the inferior quality of the radiographs taken by post-Warren investigators. In addition, these researchers were doing their work in isolation; there was neither continuity nor pooling of their efforts. Further, the diagnostic criteria that had emerged from published studies required more extensive experience in roentgenographic interpretation than most physicians could offer. Finally, in most of these studies, only small groups of patients were analyzed and adequate follow-up did not occur.

#### Dr. Jacob Gershon-Cohen

Despite the waning enthusiasm that followed Warren's paper, one American emerged during the late 1930s as a notable pioneer in the field

of breast roentgenography--Dr. Jacob Gershon-Cohen. Alone and in conjunction with colleagues such as S. M. Berger, M. B. Hermel, Helen Ingleby, H. J. Isard, L. Moore, and P. J. Hodes, the contributions of Gershon-Cohen to the literature of this field were both comprehensive and copious until his death in 1971. A bibliography of his publications, too extensive to include in this history, reveals work in the areas of preoperative roentgenography of breast tumors, (41,42) screening to detect breast cancer in asymptomatic women, (43) breast pathology, (44,45) refinements of mammographic techniques, (46) secretory breast disease, (47,48) and innovations such as thermography and xerography. (49,50) As early as 1937, Gershon-Cohen was advocating the roentgenographic screening of asymptomatic women to reduce breast cancer mortality:

Any tumor that is palpable can be demonstrated in the roentgenogram. If tumors too small for detection by palpation could be revealed, the roentgen examination might become more essential in breast tumor diseases. As a matter of fact, this can already be partially realized if resort is made to serial roentgenographic studies of the normal breast in women past the age of 25. This procedure is so simple and economically practicable that it is certainly worthy of serious consideration as a measure to be taken now in the control of mammary carcinoma. (51)

According to Dr. Philip Strax of the Guttman Institute, (52) Gershon-Cohen was also a seminal influence in his field since he taught his mammographic technique to other radiologists. And as early as January, 1956, Gershon-Cohen, with colleagues M. B. Hermel and S. M. Berger, conducted a five-year screening program for asymptomatic women at Albert Einstein Medical Center in Philadelphia. (53) This was the first time that such an extensive mammographic survey of asymptomatic



women had been undertaken and successfully completed. After a thorough physical examination and medical history were completed, each of the 1,312 participating women was screened via mammogram at six-month intervals. Of these women, 1,055 actually completed the entire program; 92 were found to have benign lesions, all of which were diagnosed correctly by the roentgenologist, and 23 were found to have malignant lesions. Thirteen of these 23 were diagnosed by Gershon-Cohen as definitely malignant; 9 others were diagnosed as probably malignant. In only one instance was a malignant lesion erroneously labeled benign. The study was an extraordinary display of diagnostic accuracy. In addition, since the engineers of the study were concerned with the possible hazards of radiation, they limited each exposure to under 1.5 rads (tissue dosage). (54) (The study was subsequently continued until December, 1965, and continued to demonstrate the value of mammography as a screening tool. (55))

In view of his undeniably prolific career, Gershon-Cohen received relatively little recognition during his lifetime. With the exception of a small grant that lent partial support to his 5-year screening study, (56) he was unable to obtain the financial assistance he sought from the U.S. Public Health Service, (57) and he was largely unsuccessful in his attempts to effect the widespread approval of mammography. Why did Gershon-Cohen meet with such frustration, and what factors thwarted an earlier acceptance of mammography? The answers to these questions vary, depending on which contemporary of Gershon-Cohen provides the information. Both Dr. Arthur Holleb, (58) Senior Vice-President for Medical Affairs and Research of the American Cancer Society, and Dr. Harold Isard, (59) Chairman of the Department of Radiology at Albert Einstein Medical Center in Philadelphia, have called Gershon-Cohen "the father of mammography."



Dr. Strax lauded the quality of the mammograms of Gershon-Cohen, whom he called a man who "always had vision." (60) The early experiments of the Philadelphia radiologist with ultrasound, thermography, and xerography were also considered ahead of their time by Dr. David Sklaroff, Chairman of the Department of Radiation Therapy at Albert Einstein Medical Center, (61) and by Dr. Mortimer B. Hermel, a former colleague and head of the Jacob Gershon-Cohen Foundation. (62) Yet, Dr. Robert Egan, who introduced the technique which led to the eventual acceptance of mammography, felt that Gershon-Cohen had "given mammography a bad name" because of his "poor technique." In addition, he indicated that Gershon-Cohen "had no imagination" and "never persisted with anything." (63)

Part of the problem in evaluating his work lies in the fact that Gershon-Cohen (in conjunction with his colleagues) was constantly refining his technique in an effort to find the most effective one. Thus any appraisal of his work must be done at a specific stage in the development of his technique. However, there were certain characteristics of the radiologist's work that remained constant. According to Hermel, (64) Gershon-Cohen always distinguished between his experimental research and his screening techniques and was careful never to experiment with a new method at the expense of the safety of the women he screened in his studies. Both Hermel (65) and Rigler (66) explained that despite the more detailed quality of the mammogram produced on industrial film (later utilized by Egan), Gershon-Cohen refused to use such film. A 1965 article by Gershon-Cohen explained that he and his colleagues had given industrial film "considerable trial before abandoning it." (67)

He gave several reasons for rejecting the Egan technique, which was first publicized in 1960. (68) (See discussion at page 286.)

The main virtue of the industrial film technique derives from the finer definition afforded by this type of film. Unfortunately, this film was developed for use with inanimate material, where complete immobility of the object and length of exposure to radiation were not considerations. When used with living subjects, however, even though they are well immobilized and their respiration is temporarily suspended, the almost imperceptible jarring which stems from the cardiovascular thrust disturbs the immobility of the breast just enough to cancel out most of the excellent definition inherent in the fine grain of industrial film....

Another advantage of industrial film that makes a strong appeal to radiologists...is the wider range of grays obtainable....The flaw, however, is the need for higher kilovoltages, which result in poorer contrast in the deep, glandular portions of the breast.

The long exposure times necessary when using industrial film also pose problems. Exposures ranging from 5 to 6 seconds with totals of 1500 to 1800 MaS (millamps) can result in doses of as much as 10 roentgens to the patient's skin per examination. This is probably inconsequential for an occasional study, but it is a factor that cannot be arbitrarily dismissed if multiple examinations are to be done, as in a periodic screening program. (69)

Hermel has emphasized that Gershon-Cohen "was always attuned to the hazards of radiation." (70) This issue caused some controversy in July, 1961, after an editorial in the Journal of the American Medical Association (JAMA) remarked on the contrast between the 1.5 rad exposure in Gershon-Cohen's screening study and the 10 rad exposure of the Egan technique. (71) A subsequent letter of clarification from Egan printed in an October issue of JAMA (72) indicated that the actual tissue dosage for a two-view mammographic examination (i.e., without the axillary view) using his technique was only 1.4 rads. In the same issue of JAMA, Gershon-Cohen replied to Egan's letter that while Egan's technique utilized 6 times as much millamperage (tube current) as his own,

he (Gershon-Cohen) had overlooked the greater film target distance used by Egan. Gershon-Cohen thus concluded, "It is a pleasure to note so little difference in exposure between the 2 techniques, although, for our purposes, we incline (sic) to use the smaller exposure factors when possible." (73)

Based on interviews with his colleagues, it becomes evident that Gershon-Cohen's failure to garner widespread support for his work may be attributed to several factors rather than to any single factor. On a personal level, Gershon-Cohen was depicted as a somewhat "aristocratic" figure by Rigler. (74) Dr. Arthur Present, former Chairman of the American College of Radiology and a member of the Executive Committee of the American Cancer Society, expressed his own positive feelings toward the Philadelphia radiologist (as did nearly all of the other radiologists who were interviewed) but explained that Gershon-Cohen was not personally very popular, describing him as "rather cold and a bit uppish about what he was doing." (75) Gershon-Cohen was also independently wealthy, enjoyed a lucrative private practice, and often rode in a chauffeured limousine, (76) all of which his colleagues may have felt set him apart from their ranks. (77) Another question raised in discussions with the colleagues of Gershon-Cohen was whether or not the radiologist had been the object of anti-semitism which might have impeded the course of his career and might have been partially responsible for his inability to obtain federal support. However, none of the physicians interviewed felt that Gershon-Cohen had been the target of prejudice. Rigler pointed out that some of Gershon-Cohen's professional opponents themselves had been Jewish. (78) Shimkin added that the NCI had always been more reluctant



to lend financial support to individuals working on their own than to individuals who had strong institutional support, as did Egan at M. D. Anderson Hospital in the early 1960s. (79)

But perhaps the most important factor that accounts for the lack of support given to Gershon-Cohen's work was the inability of other radiologists to satisfactorily reproduce his technique. According to Rigler, not only did Gershon-Cohen have extensive experience in diagnostic radiology, but he also had the funds to build x-ray equipment especially designed for his mammographic research. (80) Other radiologists, who may have had less extensive experience as diagnosticians, were also working primarily out of institutions and had to depend on the same conventional equipment used for x-rays of bones and other parts of the body at these institutions. (81) Thus other radiologists were unable to obtain mammograms of the same quality as Gershon-Cohen did. Dr. Present explained that individual attempts to duplicate Gershon-Cohen's results were carried out primarily at teaching institutions and were usually unpublicized. But Present stressed that it was "word of mouth that killed mammography at that time." Surveying the overall history of developments prior to 1960, Present concluded, "The flat failure to reproduce Gershon-Cohen's work was the reason that mammography was again buried." (82) As later developments would reveal, it was reproducibility that became a crucial factor in the eventual acceptance of mammography.

During the 1950s mammography reached the lowest ebb of its popularity. The technique had fallen into disrepute despite research by Gros in France, (83) Leborgne of Uruguay, (84) whose technique was adopted in the 1950s by Gershon-Cohen (who subsequently continued to



further modify it), by Americans Pendergrass and Lane, (85) and Rigler, Johnson, Nice, and Brauti at the Minnesota Breast Detection Clinic. (86) In his 1956 text on breast disease, surgeon C. D. Haagensen wrote:

In our own clinic we have not made roentgenograms of diseased breasts. Our point of view has been that even at their best roentgenograms cannot provide decisive information. Only biopsies studied microscopically do that. Since roentgenograms add to the expense which patients have to bear, expense already too heavy, we have not thought them to be justified. (87)

It is within the context of this climate of negativism that the significance of the contribution by Egan can best be evaluated.

### The Egan Contribution

After Robert Egan had joined the staff at M. D. Anderson Hospital in Houston as a diagnostic radiologist in 1955, Gilbert Fletcher, Chairman of the Department of Radiology, suggested that he begin to do mammography. With no further help from his colleagues, Egan began to investigate the literature in the field. He tried the techniques of previous investigators such as Gershon-Cohen, Pendergrass, and Leborgne, but found that "none of them worked." (88) Drawing on his previous background in metallurgical engineering, he devised a new high millamperage, low kilovoltage technique with industrial film and used it to make prebiopsy diagnoses. Egan recalls that even after doing several sets of mammograms in which he had accurately diagnosed carcinoma, he was met by ridicule from most of his colleagues at M. D. Anderson, particularly from the surgeons, whose initial reaction had been to "give the radiologist enough rope so that he would hang himself," (89) and from the pathologists, who maintained "a smug attitude." (90) (A notable exception was pathologist H. Stephen Gallager,

who was one of Egan's early supporters.)

Egan admits that he had had a negative attitude toward the potential of mammography until he was encouraged by Dr. Edgar C. White, Chief of Surgery at M. D. Anderson, who did not share the skepticism of his colleagues in the department of surgery. Because of the low salvage rate for breast cancer patients, who were not seeking help until their malignancies had progressed to an advanced stage, White was interested in moving diagnosis to an earlier point. Egan credits surgeons in general (who were eventually convinced of the value of his technique) for keeping mammography alive and credits White in particular for his optimism and for advising Egan to include an axillary view of the breast in each set of mammograms. (91)

Despite his feelings of frustration, Egan continued to employ his technique. After taking 1,000 consecutive breast x-rays at M. D. Anderson from May, 1956, to May, 1959, he published the results in Radiology in December, 1960. (92) His study indicated that he had correctly diagnosed 238 out of 240 tumors later confirmed by biopsy. To his great surprise, he received over 15,000 individual requests for his article. (93)

Interest in mammography began to mushroom, and the idea of the team approach in which the surgeon, radiologist, and pathologist, as well as the gynecologist and family physician each play an important role, penetrated the consciousness of the medical community. "The biggest thing that came out of mammography," comments Egan, "was the team approach. The breast cancer problem is so big that it can stand any number of people as part of the team." (94) Nevertheless, it took several more years before mammography was accepted among the majority of Egan's peers.

Hoping to conduct another study, Egan submitted to the regional branch of the U.S. Public Health Service a proposal and request for support which was channeled as a matter of course to Dr. Lewis C. Robbins, Chief of the Cancer Control Program. (95) Robbins had been alerted to the potential of mammography in 1957 when he had discussed with I. S. Ravdin, an internationally renowned Philadelphia surgeon, the experiences of Jacob Gershon-Cohen, who had been finding cancer in asymptomatic patients via mammography. (96,97) (Ravdin himself originally had been a vocal opponent of Gershon-Cohen's technique and had been a member of the National Cancer Advisory Council that had refused to lend financial support to his research in the 1940s. (98) However, after visiting with Gershon-Cohen, Ravdin became a promoter of the radiologist's work in the late 1950s after Gershon-Cohen had been able to find non-palpable tumors (microcalcifications) that Ravdin had been unable to diagnose in the breasts of several of his own patients. (99))

But despite his awareness of Gershon-Cohen's research, Robbins had remained skeptical, and the federal support requested by the radiologist was not given to him. What was it that made Robbins more receptive to the work of Egan? Egan had been diagnosing women already suspected of having breast problems. In contrast, Gershon-Cohen had been screening asymptomatic women since 1956 (100) and his thinking, according to Shimkin, was thus much more geared to the public health concern with early diagnosis than was Egan's study. (101) Yet Robbins chose to support the work of Egan. Shimkin, formerly with the National Cancer Institute himself, explained that there was a ripeness in the circumstances surrounding Egan's work that did not exist during the time



of Gershon-Cohen's research in the 1950s. At the time of the Egan study, the Cancer Control branch of the U.S. Public Health Service was looking for projects to fund, and by 1960, the contract mechanism had been introduced by NCI Director Dr. Kenneth Endicott whereby federal support could more easily be given to new research. (102) Moreover, after its publication the 1960 study by Egan had been wholeheartedly supported by the prestigious M. D. Anderson Hospital, which did a considerable amount of "drum beating" to create a favorable climate for Egan's new technique. (103) Such backing was not given to Gershon-Cohen's work by Albert Einstein Medical Center since much of the radiologist's work was undertaken on his own initiative and funds.

On a purely technical level, an analysis of the literature describing their respective techniques in 1961 reveals the following differences between the mammography of Gershon-Cohen and Egan.

(Measurements are for craniocaudad and mediolateral views of the breast and do not include the axillary view.)

	<u>Egan</u> (104,105)	<u>Gershon-Cohen</u> (106)
Film	Kodak Industrial X-Ray Type M or AA	Non-screen film
(Tube Current) MA	250-300	100
(Tube Voltage) KV	26-28	23-32
(Exposure) Time	6 seconds	1-3 seconds
(Target Film) Distance	36 inches	14 inches

At the Sixth Annual Mammography Conference in 1967, Dr. Simon M. Berger, who had conducted the mammography screening survey with Gershon-Cohen at Albert Einstein Medical Center, commented on the differences between the technique used in the survey and the Egan technique:



We had the problem of devising and evaluating a technique primarily for our survey group.....

.....  
...The admitted advantages of less distortion obtained by longer target film distance and the preferable film type of M and AA is offset by the blurring of longer time exposures. This, plus the necessity of a low patient x-ray exposure dose governed our decision on the type of technique employed.

.....  
In conclusion, we do not get the clarity of objects that Dr. Egan can get. ... It's the difference between being willing to put up with a Cadillac or a Chevrolet. I have lived a Chevrolet life; I have found it quite adequate. I would like to make the point that the difference in the technique is not such a factor as some indicate. If we are dedicated mammographers, we will evolve a good technique....(107)

Thus it is possible to conclude that it was the reproducibility of the Egan technique compared to that of the Gershon-Cohen technique which finally garnered Robbins' willingness to lend federal support to Egan's work. (108) According to Robbins, he had visited Egan in Houston in February of 1961 to appraise his work but "was not impressed" on his first visit. A month later, however, Robbins returned to Houston and by chance met a community radiologist from Ohio who changed Robbins' opinion.

...when I was with Egan at M. D. Anderson, I met a man who had paid his own way from Ravenna, Ohio, just outside of Cleveland. He had spent a week with Egan. I saw him on Friday of that week. I asked him, 'Can you see any cancer in there?' He said, 'Oh, yes, I'm finding cancer Egan couldn't find even on his own cases.' He showed me how to improve the perception. I asked him, 'Do you think you could do them back home?' 'Oh, yes,' he said, 'I will have no trouble.'

Suddenly I could see radiologists all over the country learning this within a short period of time and doing it. I came back and asked five men to go to Houston; I would pay their way. They were Jim Cooney, Medical Director of the Cancer Society, Ted Hilbish, Cancer Institute Radiologist, Tom Carlile and two other men, top men in the country, Eugene Pendergrass and Wendell Scott. When the five of them came back, Scotty told me, 'I had

looked at mammography before, but what I saw down there is a quality I have never seen before. ...' (109)

Based on the observations of his team and what they had heard from Dr. R. Lee Clark, Director of M. D. Anderson, Edgar C. White, Stephen Gallager, and others at the hospital, and sparked by the enthusiasm of the Ohio radiologist, Robbins sensed the potential of the Egan technique. (110) He decided to determine if it could be reproduced at other institutions and if others could be trained to do mammography using the team approach. After calling in statistician Harvey Geller from the Cancer Control Program, Robbins suggested a revolutionary reproducibility study of mammography which would be conducted at 12 institutions in Texas and at 12 others across the United States. The project's advisory committee, co-chaired by radiologist Wendell Scott and pathologist David Wood, included radiologist Thomas Carlile, surgeon Murray Copeland, surgeon Warren Cole, general practitioner John Paul Lindsay, and surgeon Harry Nelson, with Bill Melton, at that time a hospital administrator, brought in from South Carolina to direct the project.

After much work by Egan, Melton, Geller, and Lindsay to coordinate the efforts of the cooperating institutions, the project began. Valuable technical assistance was rendered by Endicott, Director of the National Cancer Institute, Shimkin, Director of NCI's Field Studies, and Eleanor Macdonald, statistician at M. D. Anderson. (111) (As early as 1962, Shimkin proposed a randomized study to compare survival rates of women with and without mammography, but he had been advised by Endicott to wait until the results of the reproducibility study were known.) (112) Under the division of responsibility for the study, M. D. Anderson would

train radiologists and serve as the clinical center of the study, the Cancer Control Program would collect data and provide statistical evaluation, and the National Cancer Institute would assist with analysis of the data. (113)

The results of the reproducibility study, completed in 1964, were published in February, 1965, and indicated that radiologists with five days of training could satisfactorily perform the Egan technique. (114) The institutions that had participated in the study had detected 79 percent of the breast lesions later shown to be malignant and 90 percent of the lesions found to be non-malignant after biopsy (i.e., 10 percent had been incorrectly identified as malignant on the mammograms.)

In addition to these results, the project had generated the first two annual mammography conferences, which have been held every year since 1962. (115) The publication of the study also included the first national endorsement of the Egan technique, which came from Surgeon General Luther L. Terry. His statement, appended to the reproducibility study, was as follows: "Mammography shows promise of being an important diagnostic aid in control of cancer of the breast. Lack of knowledge of what the technic offers tends to impede continued development and professional acceptance of mammography." (116) Based on the results of the reproducibility study and the other recommendations of his advisory committee, Terry had felt that the Egan technique was "a step forward" and had hoped that his endorsement would promote further acceptance of mammography by members of the medical profession. (117)

Since those who had devised the reproducibility study realized the importance of adequate training of the disseminators of the Egan technique, some of the centers chosen for the study had also been designated



as training centers, with teaching aids financed by the Cancer Control Program. However, by 1963, the training project was faltering as a result of problems with changes of personnel and snags in the pathology and biopsy processes at various institutions. (118) To revitalize the training concept, physicians James V. Rogers and R. Waldo Powell of Emory University formulated and carried out a training program in mammography and breast diseases to run from July, 1963, to June, 1965, at 16 southeastern institutions, thereby establishing the Egan technique even more firmly. (119,120)

During the early 1960s, the American College of Radiology (ACR) had made no formal statement about the new Egan technique, which at the time was generating a great deal of controversy. (Egan himself notes that he had been blackballed for fellowship in the ACR during this period.) (121,122) Reluctant to prematurely endorse the new technique, Dr. Present, Chairman of the ACR at that time, was persuaded by Thomas Carlile, President of the American Cancer Society, and by surgeon Murray Copeland to create an ad hoc mammography committee to examine this new development. Headed by Present, the committee convinced the College to support the mammography program, which was formally endorsed by ACR in July, 1964. (123) In an effort to get a definitive evaluation of mammography, the ACR held its first Standardization Conference, in conjunction with the Cancer Control Program, in February, 1965, in Philadelphia. According to Robbins, (124) who participated in the conference, there were several reasons for the meeting:

1. the need to create a basic training program in mammography for radiologists;
2. the wide divergence in the application of mammography and the publication of different techniques creating confusion within



the profession;

3. the need to define a minimal mammographic technique and to determine what variations would be acceptable; and,
4. the need for a conference on mammography to demonstrate the utility of a conference as a mechanism toward achieving standardization and a possible resolution of other radiological issues. (125)

Participants included radiologists, surgeons, gynecologists, biophysicists, technologists, and x-ray equipment and film manufacturers.

Each group met separately and was asked to arrive at conclusions on all facets of mammography that applied to their respective fields. After two-and-a-half days, the groups emerged and pooled their opinions, which Present summarized: "There are no great disagreements about skin dosage or about techniques in mammography; mammography contributes to cancer control and has the potential of reducing the death rate of cancer of the breast." (126)

The conference had recognized that the interest of surgeons in mammography would only be developed by demonstrating that "quality management" of breast disease requires mammography. (127) Conference members also stressed that if mammographic screening were to be promoted by radiologists, they must insure that all technicians and radiologists must be trained in the best mammographic techniques. (128) Meetings held between physicists, radiologists, and manufacturers of x-ray film and equipment resulted in recommendations for the further development of better x-ray tubes and film processing and stressed the need for faster film and lower kilovoltage. Representatives from film and equipment companies emphasized that if screening were to be the diagnostic procedure of the future, commercial interests must be informed of the needs

of the medical profession so that money and effort could be invested in time to meet those needs. (129)

The Ad Hoc Committee decided to withhold mass publicity of its endorsement of mammography until the radiologists were sure that the Egan technique was reproducible and that competent technicians could be trained. (130) Dr. Present, who had previously obtained federal money so that the ACR could mail to all radiologists the 1962 edition of the Cancer Bulletin devoted to mammography and the reproducibility study, was again able to secure federal funding from Lewis Robbins to establish 13 centers to train mammographers. (131) In 1970, the federal government discontinued its support of the training center program, which was subsequently taken over by the Mammography Committee of the ACR, headed initially by Present, then by Wendell Scott and Richard Lester. (132) Underwritten by a federal grant, the ACR has since prepared numerous training packages using the latest audiovisual methods to teach a multi-modality approach to breast cancer detection--physical examination, mammography, and thermography in all of their clinical and technical aspects. (133) According to Present, after ACR had laid all of the groundwork for these training centers, the government decided that it would choose the centers instead. Currently, the status of the project is such that the ACR acts only in an advisory capacity. (134)

Asked to evaluate the reasons why the Egan technique met with such success, Present cited Egan's innovative modifications of prior techniques, especially his use of industrial film. (135) In addition, Present explained, Egan had the prestige of M. D. Anderson Hospital behind him, as well as the enthusiasm of Lewis Robbins and respected

physicians such as Wendell Scott, Murray Copeland, and Thomas Carlile. All of these factors, combined with the success of the reproducibility study, led to the acceptance of Egan's technique. (136)

#### The Application of Mammography to Mass Screening Programs

After the publication in 1960 of Egan's experiences at M. D. Anderson, Dr. Philip Strax began to speculate about the effect mammography might have on the high breast cancer mortality rate. (137) To answer this question, a screening program was formulated by Strax and his colleagues Sam Shapiro, Director of the Department of Research and Statistics of the pre-paid group practice Health Insurance Plan of Greater New York, and Dr. Louis Venet, Associate Director of Surgery and Chief of the Breast Service at Beth Israel Medical Center in New York. Others who collaborated on the design of the study were Michael Shimkin, Director of NCI Field Studies, Jacob Gershon-Cohen, and Robert Egan. (138) The five-year program, known as the Health Insurance Plan (HIP) study, began in December, 1963, under a contract with the National Cancer Institute, which also gave some advisory assistance to the study. (According to Shimkin, the study required little statistical or technical aid from NCI since, as a result of the efforts of Sam Shapiro, the project was "smooth running" in these areas.) (139) The study was attractive to NCI because it was carefully controlled research which apparently would prove or disprove the value of screening as an early detection device and as a way to reduce the breast cancer mortality rate. (140) The investigation focused on 62,000 women aged 40-64 who were paired and randomly divided between a control group, which was not



screened, and a study group which participated in a breast cancer screening program employing mammography and clinical examinations. The program included an initial examination, three complete follow-up studies at annual intervals, and later follow-up without further screening. After compiling the data collected over five years, Strax, Shapiro, and Venet discovered that among women aged 50 and over the breast cancer mortality rate of the study group was one-third lower than that of the control group. However, the mortality rates among women under 50 in the two groups were the same. (141,142) The seven-year follow-up of the two groups, in which the total number of cancers in each group were nearly equal, indicated only 70 breast cancer deaths in the study group compared with 108 deaths in the control group. (143) Shapiro, Strax, and Venet are now in the process of collecting further data and plan to do a ten-year follow-up. According to Dr. Strax, the HIP investigators hope to find that the reduction in mortality has persisted. "Then we can say we have cured women," he emphasized. (144)

The most ambitious screening program since the HIP study has been the ACS-NCI Breast Cancer Detection Demonstration Project (BCDDP). The history of that project began when Philip Strax suggested to Arthur Holleb that the American Cancer Society take a more active part in breast cancer screening. (145) Holleb agreed, and the issue was subsequently discussed at a 1971 meeting of an ACS Survey Committee comprised of senior volunteers. Holleb recalls:

This is when we said we think we should plan breast cancer detection demonstration projects for mammography, thermography, teaching of breast self-examination, and physical examination of a selective populace over a five-year period, if we can get the money to do it.



They immediately said we have a million dollars a year for each two years to start this program off. We decided to do 12 programs, not as a clinical investigation project, but as a service program and nothing more. (146)

In February, 1972, the board of directors of the ACS approved a program to establish the 12 centers. (147) According to a recent article in Science, "It was shortly after this plan was drawn that cancer control money became available to the NCI. So, in September 1972, Cancer Society officials went to NCI with a proposal for a joint, and much larger, breast cancer screening program." (148) The proposal was for joint funding and the ACS pledged to make significant contributions not only in financial terms, but with volunteers participating as secretaries, appointment makers, and in other necessary roles to maintain the centers and help reduce the cost of operation. (149)

Agreement was reached for joint sponsorship and expansion of the project, but not without some hesitation on the part of the National Cancer Institute. Holleb explains, "[Dr. John] Bailar (the Acting Director of Cancer Control at this time) was totally disinterested, and he wanted no part of it. No reason was expressed." (150) In retrospect, Bailar's reluctance is not surprising in view of his opinions on the risks of mammography which were expressed in January, 1976, in a controversial article (151) discussed infra at page 300.

How did ACS get NCI's cooperation? The final decision appears to have been made by NCI director Dr. Frank Rauscher. Holleb remembers:

Again, I reached the point of utter frustration...at one of our board meetings with Alan Davis, Dick Rauscher, and I....I said to Dick that the time has come when we either are going to move ahead in the American Cancer Society Program (by ourselves) or you're going to join us. He said, 'Tell me why you think this is a beneficial program,'

and I did. And he said, 'We're going to do it. We will join you.' (152)

Rauscher has recounted that the following factors led to his decision:

- Breast cancer is a major killer of women.
- There have been significant advances in mammographic technique (such as lower dosages of radiation).
- The HIP study unequivocally demonstrated that the addition of mammography to routine check-ups is of real benefit to women over the age of 50.
- Women less than 50 years of age would be included in the screening program in hope of discovering that there is some benefit to them. (153)  
(Note: Since the program was to be a service program rather than a scientific study, it is not clear how this issue was to be resolved.)

The ACS screened applications from various institutions proposing to establish a screening program (primarily to assure full support of the local ACS division) and sent them on to the NCI for review and recommendations for funding. Dr. Nathaniel Berlin, Director of the Division of Cancer Biology and Diagnosis at the time, was given administrative responsibility for the proposal review and selection process, which he carried out by using his Extramural Diagnostic Research Advisory Group as the formal review body. (154) Unlike Bailar, Berlin was supportive of the project at the time it had been first proposed to NCI and had expressed to Rauscher his positive feelings about the proposed study. According to Holleb, "He (Berlin) deserves very special mention in this thing because Nat was very sympathetic to the idea of getting the federal government involved in this as well. Berlin was enthusiastic about it. He could not get Bailar to participate in any way. Berlin did not have the money for it; the money was in John Bailar's hands." (155)\*

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\*(For another view of the decision-making process behind the project, see

After the genesis of the program, it was clear that it was going to be one of the most visible programs of the American Cancer Society and the National Cancer Institute. As a result, the number of centers was increased to 27. (156) (After the NCI had joined the ACS in sponsoring the program, the number of centers had been expanded from 12 to 20--5 in each ACS geographic region.)

The goal of the Breast Cancer Detection Demonstration Project is to annually screen 270,000 women at ages 35 and above, using a multi-modality approach--detailed medical history, physical examination, the teaching of breast self-examination, mammography, and thermography. Data from each center are sent with data from the other 26 centers to a national computer center in Philadelphia. The patient's physician is notified of positive findings, and the patient is then contacted to assure proper treatment and follow-up. Physicians are urged to furnish further follow-up information to the Project, and pathologists are asked to submit biopsy data to the pathologist at the detection center. (157,158) As of March, 1976, 245,000 women had been screened, and clinics were finding 6 breast cancer cases per 1,000 women, according to Dr. Benjamin Byrd, Jr., president of the ACS. (159) Seventy percent of these cancers have been found in the over-50 population. More important, 75 percent of these women were discovered to be free of lymph node involvement, which factor appreciably increases survival rates and is "a complete reversal of the normal hospital population," according to Holleb. (160) The Breast Cancer Detection Demonstration Project has also discovered 30 percent of its cancers in

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"X-Ray Mammography--Background to a Decision," by Daniel S. Greenberg in the New England Medical Journal, vol. 295, no. 13, 739-40, September 23, 1976.)



women under 50. Among the 600 cases of breast cancer detected among this younger population, not one woman had died, and only two women had had a recurrence of their disease following treatment, as of April, 1976. (161)

The most vocal criticism of the ACS-NCI project has come from Dr. John C. Bailar III, editor of the Journal of the National Cancer Institute, who has charged that radiation exposure during repeated annual mammographic screening may cause more cancer than it detects. (162) At Bailar's request, the NCI appointed three committees of pathologists, epidemiologists, and radiologists to investigate this issue. But Arthur Holleb of the ACS has emphasized that NCI's actions should be interpreted as an inquiry, not as an admission of guilt on the part of NCI. (163) Arthur Present, director of one of the 27 demonstration projects, has cited the value of screening and has questioned the validity of Bailar's argument. Present asserted that Bailar's data are "extrapolations from two very non-applicable statistics" and that Bailar used figures from Hiroshima (where large amounts of radiation were involved) and from fluoroscopy, which used high-powered, unfiltered x-rays. (164) Present indicated that according to the U.S. Bureau of Radiological Health, in women aged 35-50, the chance of inducing cancer by modern annual mammography is 2.4 per million; in women above 50 it is 1 per million. (165) He added that the ACS-NCI project is finding 8,000 occult carcinomas for each million asymptomatic women screened. Thus the risk factor is 2.4 compared to 8,000. Present feels that these figures have not been publicized sufficiently to refute Bailar's charges. Summarizing the radiation controversy, Present said, "There is no proof on



either side. All we can say is there is no reason to believe Bailer's statements are correct." (166)

Despite data that tend to rebut Bailer's remarks, attention given to the controversy by the media had an impact on the Demonstration Project. "We lost a lot of women," commented Holleb. (167) In response to the situation, the National Cancer Institute established three ad hoc groups to examine the evidence on mammography, one approaching it from the standpoint of pathology, another radiation biology, and the third epidemiology. The last group reported in July, 1976, that based on the findings of the Health Insurance Plan study (see discussion at page 295), the use of mammography to screen women over 50 is justified if the radiation dose to breast tissue can be kept below 1 rad. (168) The committee recommended:

The discontinuation of mammography for routine screening of women under 50;

The standardization of radiation exposure in mammography at 'the lowest level consistent with satisfactory determination of the likelihood of breast cancer;'

The prompt undertaking of further clinical trials 'to ascertain more precisely the value of mammography in relation to other means of detecting breast cancer including conversion of the Breast Cancer Detection Program to such a trial.' (169)

The controversy about the Breast Cancer Detection Demonstration Project was rekindled after a November, 1976, report by Ralph Nader's Health Research Group stressed the need for a new consent form that would provide more information on the risks of mammography to participants in the screening program. (170) The report also indicated that since some of the mammography machines used at certain Project

centers were still emitting radiation in excess of the recommended dosage for the study (i.e., 1 rad of tissue dosage), the program of strict surveillance of the Project's mammography equipment recently implemented by NCI should be expanded. (171)

In an effort to increase the feasibility of mass screening, numerous radiologists have been developing mammographic techniques which further reduce radiation dosages. A new microdose technique developed by Dr. M. B. Hermel and Dr. M. G. Murdock of Jefferson Medical College in Philadelphia cuts doses to a range of from .45 to .9 Rads of skin radiation per exposure. (172) This compares very favorably with the dose levels administered in connection with the Breast Cancer Detection Demonstration Project, presumably limited to 2.5 Rads (skin dosage). (173) Meanwhile, Philip Strax and colleagues Dr. Norman Malsky and Dr. Norman Strax have devised automated millirad mammography using rare earth screens with a reduction of skin exposures to .3 Rads or less. (174) The search for improved techniques is becoming an increasingly popular area of research, as evidenced by the numerous papers--more than 22--presented on this topic at the Third International Symposium on Detection and Prevention of Cancer in New York in April, 1976. In addition, it is anticipated that the introduction of "lo-dose" film by Eastman Kodak and Dupont will help to drastically cut radiation exposure.

#### Other Screening Technologies

Over the past two decades, other techniques have been developed by investigators in order to find more effective screening tools for

breast cancer. Three of these techniques--xeroradiography, thermography, and ultrasonography, have received considerable attention, although none of these has gained the acceptance that mammography has been accorded.

Xeroradiography was developed originally by Ruzicka and his colleagues. (175) Extensive work with the technique was later done by Wolfe. (176,177,178) Xeroradiography makes use of a selenium-coated aluminum plate instead of conventional film and seems to be gaining acceptance in current medical practice. However, controversy still exists about the quality of the xeroradiographic image. (179) In addition, the equipment used in the process, though relatively expensive, has thus far been subject to frequent mechanical failures. (180)

Thermography, based on the principle that skin temperature over a tumor will be higher than that of the surrounding area, gives a pictorial record of the temperature distribution of the breast. Developed by Lawson (181) and further investigated by Lloyd Williams and Handley, (182) the technique presents diagnostic difficulties because of temperature differences among normal women and because benign and malignant lesions are not easily distinguished. It has thus far been advocated primarily as a supplement to rather than as a replacement for mammography.

Finally, ultrasonography, used first on human stomach tissue by Wild (183) and later on human breast tissue by Wild with Neal (184) and Reid, (185) is a scan of the patient's breasts, which are immersed in water, with ultrasonic beams. Echoes are recorded on a cathode ray oscilloscope and then on polaroid film. A solid lesion within the breast



reflects ultrasound; thus, an increased number of echoes is expected at the site of the tumor. But, because ultrasound does not adequately distinguish between solid and cystic lesions, the technique has received very few endorsements.

While a great deal of professional attention has been focused on technical improvements in screening for breast cancer, the screening concept itself raises other issues. Since limited manpower and funds prohibit the rapid spread of such programs, it is important to decide which populations of women would derive the greatest benefit from such projects. One question that has been asked is whether or not screening should be limited to women aged 50 and above. While the HIP study indicated that such a limitation may be valid, the ACS-NCI Demonstration Project has detected 30 percent of its cancers in women under 50. (186) Another issue raised is the frequency of screening. Based on the HIP study, one-year intervals increase lead time from 11 to 13 months. (187) While the future HIP follow-up may indicate a revision in this data, it is still estimated that the interval for screening will probably be one year and will certainly be no more than two years. (188) A third area of concern has been the identification of women with a high risk of breast cancer. Shapiro has observed that "our knowledge is still inadequate to identify a high risk group which accounts for most of the breast cancers diagnosed." (189) Among risk factors that have received attention thus far are socio-economic differences, pregnancy and menstrual histories, family history, prior benign breast conditions, and hormonal profiles derived from analyses of blood plasma. (190,191)

Dr. Robert Egan has also turned his attention to this area of research. In 1962, supported in part by an NCI grant, Egan and his



colleagues at Emory University designed a project to obtain prospective data for breast studies. The data were to be collated and analyzed by discriminant functions to place patients into cancer or non-cancer populations on the basis of patterns of risk factors rather than on the basis of a single risk factor. The study, which has not yet been published, (192) indicates that risk factors in combination, based on clinical and radiological data, can be used to effectively identify high- and low-risk patients. Thus a smaller percentage of the population would need to be studied to define a high-risk group that would derive the maximum benefit from screening. (193)

#### The History of Mammography: A Retrospective View

It is evident from the previous chapter that the history of mammography has not been uneventful. However, while the development of this technique may be characterized as evolutionary rather than revolutionary, the evolution has not been a steady one: for the most part, the forces which have inhibited the refinement and implementation of mammography have been more numerous than those which have promoted it. In the course of this uneven history the following factors emerge as most significant.

--The breast cancer problem existed for many years before the medical profession added it to the agenda of its concerns. The steadily increasing breast cancer mortality rate in the early decades of this century apparently was not considered noteworthy by American physicians. Thus, the investigation of breast disease in this country was not pursued with diligence until the late 1930s.

--It appears that there was no exchange of knowledge about breast diseases among early American and European researchers, who preceded the Americans in their use of the x-ray as an aid in breast research. After Salomon published his findings in Germany in 1913, it was 17 years before news of Warren's fortuitous discovery of the x-ray's diagnostic potential reached the American medical community.

--The development of mammography might possibly have begun in the late 1930s after the early recognition by Gershon-Cohen of the value of the technique for purposes of diagnosis and screening. However, the significance of Gershon-Cohen's work was obscured by his lack of popularity (perhaps even his lack of "salesmanship" of his technique) among some of his colleagues and by the failure of other radiologists to satisfactorily reproduce his results. The latter factor may have militated strongly against federal support of Gershon-Cohen's projects.

--The skepticism and professional partisanship of surgeons and pathologists created an atmosphere of negativism and divisiveness which impeded the earlier investigation and acceptance of breast radiography.

--The support and insight of Lewis C. Robbins was crucial to the acceptance of mammography in general and of the Egan technique in particular. Robbins' successful efforts to design and obtain federal support for a reproducibility study led to the discovery that even community radiologists could learn and apply Egan's method, which might not have been adopted as readily in the absence of such a study.

--Problems that have occurred with the ACS-NCI Breast Cancer Detection Demonstration Project indicate that the eagerness of the federal

government to actively promote mammography as a screening device might have been tempered with more caution. Had the approval of the undertaking been preceded by a more thorough analysis and evaluation of its design, some of the current difficulties with the project might have been avoided.

Whether or not the previous factors have exerted a positive or negative influence, it is undeniable that mammography has changed our way of thinking about the breast cancer problem. However, it is too early to know whether time will bear out Dr. Holleb's optimistic speculation: "If we educate the physician and the public about the need for earlier diagnosis of breast cancer--trying to find it before it's palpable and indicating to physicians, both surgeons and diagnostic radiologists, that it's possible to do this with modern technology, we may have achieved something similar to what happened with the Pap smear." (194)

## Chronology of Significant Events in the History of Mammography

- 1896      Roentgen announces his invention of the "x-ray."
- 1913      Salomon takes the first roentgen ray pictures of the breast and describes the most common forms of mammary cancer.
- 1930      Stafford L. Warren is the first American to demonstrate that preoperative roentgenography of the breast has diagnostic value.
- 1937      Gershon-Cohen (with A. E. Colcher) advocates the use of roentgenographic screening of asymptomatic women to reduce breast cancer mortality.
- 1956      Gershon-Cohen, M. B. Hermel, and S. M. Berger begin a five-year screening study at Albert Einstein Medical Center which later demonstrates that periodic mammograms can be used to detect and correctly diagnose breast lesions in asymptomatic women.
- 1960      Study by Egan indicates that by using his new mammographic technique he could accurately diagnose 238 out of 240 breast tumors later confirmed by biopsy at M. D. Anderson Hospital.
- 1961      A federally funded study to test the reproducibility of the Egan technique is proposed by Dr. Lewis C. Robbins, Chief of the Cancer Control Program of the U.S. Public Health Service.
- 1962      The First Annual Mammography Seminar is held in Houston, Texas.
- 1963      Shapiro, Strax, and Venet initiate the Health Insurance Plan study.
- 1965      Results of the reproducibility study indicate that radiologists with five days of training could satisfactorily perform the Egan technique with a high degree of diagnostic accuracy.
- 1965      U.S. Surgeon General Luther L. Terry endorses mammography as a promising diagnostic tool.
- 1965      At its first Standardization Conference, the American College of Radiology recognizes that mammography can potentially reduce the breast cancer mortality rate and that mammography training centers should be established to insure the quality of the technique.
- 1969      Shapiro, Strax, and Venet announce the five-year findings of the Health Insurance Plan study in which screening, including mammography, reduced by one third the breast cancer mortality rate in women over 50.
- 1973      Inception of the ACS-NCI Breast Cancer Demonstration Project.



- ( 1) Statistics supplied by Mr. Edwin Silverberg, Project Statistician for the American Cancer Society, New York City, New York.
- ( 2) See note (1).
- ( 3) The population of Albuquerque was 297,451 in 1970, according to The County and City Data Book, U.S. Department of Commerce, Social and Economic Statistics Administration, Bureau of the Census, 1972.
- ( 4) Cancer Rates and Risks, 2nd ed. Biometry Branch, National Cancer Institute, 1974, pp. 14 and 16, Table 6 and Figure 7.
- ( 5) See note (4) at 90-91, Tables 26 and 27.
- ( 6) See note (1).
- ( 7) Warren, S.L.: A roentgenologic study of the breast. Am. J. Roentgenol. and Rad. Therapy 24: 113-124, 1930.
- ( 8) Clark, R.L., Copeland, M.M., Egan, R.L., et al: Reproducibility of the technique of mammography (Egan) for cancer of the breast. Am. J. Surg. 109:127-133, 1965, at 127.
- ( 9) Salomon, A.: Beiträge zur Pathologie and Klinik der Mammocarcinome. Arch. f. klin. Chir. 102:573-668, 1913.
- (10) Gershon-Cohen, J.: Breast roentgenology: historical review. Am. J. Roentgenol., Rad. Therapy & Nuc. Med. 86:879-883, 1961, at 879.
- (11) Egan, R.L.: "History of Mammography" in Mammography, 2nd ed. Springfield, Ill., Charles C. Thomas, 1972, pp. 3-22.
- (12) Goyanes, J., Gentil, F., Guedes, B.: Radiography of mammary gland and its diagnostic value. Arch. Espano de Oncol. 11:111-142, 1931.
- (13) See note (10) at 880.
- (14) Vogel, W.: Die Röntgendarstellung von Mammatumoren. Arch. f. klin. Chir. 171:618-626, 1932.
- (15) See note (10) at 880.
- (16) See note (10) at 880.
- (17) Finsterbusch, R., Gross, F.: Kalkablagerungen in den Milch-und Ausführungsgängen beider Brustdrüsen. Röntgenpraxis 6:172-174, 1934.
- (18) See note (10) at 880.

- (19) Telephone interview with Dr. Stafford L. Warren, founding dean of the medical school of the University of California at Los Angeles and former medical director of the Atomic Energy Commission, by Myrna Morganstern of HCCP, May 18, 1976, Los Angeles, Ca.
- (20) See note (7).
- (21) See note (7) at 124.
- (22) See note (19).
- (23) Shimkin, M.B.: Soldiers of St. Agatha: some campaigns against breast disease. Fourth Wendell G. Scott Memorial Lecture, March 10, 1976. Text courtesy of Dr. Shimkin.
- (24) Telephone interview with Dr. Michael B. Shimkin, Professor of Community Medicine and Oncology at the University of California at San Diego School of Medicine, by Myrna Morganstern of HCCP, August 9, 1976, San Diego, Ca.
- (25) Interview with Dr. Leo Rigler, Emeritus Professor of Radiological Sciences at the University of California at Los Angeles, by Myrna Morganstern of HCCP, August 12, 1976, Los Angeles, Ca.
- (26) See note (19).
- (27) See note (19).
- (28) Seabold, P.S.: Diagnosis of breast diseases by X-ray. Ann. Surg. 94:443-444, 1931.
- (29) Seabold, P.S.: Roentgenographic diagnosis of diseases of the breast. Surg., Gynec., & Obstet. 53:461-468, 1931.
- (30) Seabold, P.S.: Procedure in roentgen study of the breast. Am. J. Roentgenol. & Rad. Therapy 29:850-851, 1933.
- (31) Riemann, S.P., Seabold, P.S.: Correlation of X-ray picture with histology in certain breast lesions. Am. J. Cancer 17:34-41, 1933.
- (32) Lockwood, I.H.: Roentgen ray study of mammary gland. South. M. J. 25:903-907, 1932.
- (33) Lockwood, I.H.: Roentgen-ray evaluation of breast symptoms. Am. J. Roentgenol. & Rad. Therapy 29:145-155, 1933.
- (34) Lockwood, I.H., Stewart, W.: Roentgen study of physiologic and pathologic changes in mammary gland. J.A.M.A. 99:1461-1466, 1932.
- (35) Dominguez, C.M.: Estudio radiológico de los descalcificadores. Bol. de la Soc. de Anatomia Patologica 1:175-180, 1930.

- (36) Baraldi, A.: Roentgen-neumo-mastia. Rev. de cir. de Buenos Aires 14: 321-342, 1935.
- (37) Hicken, N.F.: Mammography: roentgenographic diagnosis of breast tumors by means of contrast media. Surg., Gynec., & Obstet. 64:593-603, 1937.
- (38) Espaillat, A.: Contribution à l'étude radiographique du sein normal et pathologique. Thèse de Paris, No. 417, Librairie Paris, 1933.
- (39) Gunsett, A., Sichel, D.: Sur la valeur pratique de la radiographie du sein. J. de radiol. et d'électrol. 18:611-614, 1934.
- (40) See note (10) at 881 and note (11) at 4.
- (41) Gershon-Cohen, J., Hodes, P.J.: Tumors of the breast: preoperative roentgenography. Surg., Gynec., & Obstet. 86:723-728, 1948.
- (42) Gershon-Cohen, J., Ingleby, H., Hermel, M.B., et al: Accuracy of pre-operative X-ray diagnosis of breast tumor. Surgery 35:766-771, 1954.
- (43) Gershon-Cohen, J., Ingleby, H., Moore, L.: Can mass X-ray surveys be used in detection of early cancer of the breast? J.A.M.A. 161:1069-1071, 1956.
- (44) Gershon-Cohen, J.: Some contributions of radiology to pathology of female breast. Brit. J. Radiol. 26:87-92, 1953.
- (45) Gershon-Cohen, J., Ingleby, H.: The roentgenology and pathology of cyclic disturbances in the breast. Surg., Gynec., & Obstet. 94:91-102, 1952.
- (46) Gershon-Cohen, J.: Chest cradle for roentgen examination of female breast. Radiology 28:234-236, 1937.
- (47) Gershon-Cohen, J., Ingleby, H.: Secretory disease and plasma cell mastitis in the female breast. Surg., Gynec., & Obstet. 95:479-504, 1952.
- (48) Gershon-Cohen, J., Ingleby, H., Hermel, M.B.: Calcification in secretory disease of the breast. Am. J. Roentgenol., Rad. Therapy & Nuc. Med. 76: 132-135, 1956.
- (49) Gershon-Cohen, J. Mammography, Thermography and Xerography. Cancer J. Clin. 17:108-112, 1967.
- (50) Gershon-Cohen, J., Berger, S.M., Haberman, J.D., et al: Advances in thermography and mammography. Ann. N.Y. Acad. Sci. 121:288-300, 1964.
- (51) Gershon-Cohen, J. Colcher, A.E.: Evaluation of roentgen diagnosis of early carcinoma of the breast. J.A.M.A. 108:867-871, 1937, at 868-869.
- (52) Interview with Dr. Philip Strax of the Guttman Institute by Myrna Morganstern of HCCP, April 26, 1976, New York City.

- (53) Gershon-Cohen, J., Hermel, M.B., Berger, S.M.: Detection of breast cancer by periodic X-ray examinations. J.A.M.A. 176:1114-1116, 1961.
- (54) See note (53) at 1116.
- (55) Gershon-Cohen, J., Ingleby, H., Berger, S.M., et al: Mammographic screening for breast cancer. Radiology 88:663-667, 1967.
- (56) See note (25).
- (57) See notes (52), (62), and (96).
- (58) Interview with Dr. Arthur Holleb, Sr. Vice-President for Medical Affairs and Research of the American Cancer Society, by Devra Breslow of HCCP, April 29, 1976, New York City.
- (59) Telephone interview with Dr. Harold Isard, Chairman of the Department of Radiology at Albert Einstein Medical Center, by Myrna Morangstern of HCCP, April 27, 1976, Philadelphia, Pa.
- (60) See note (52).
- (61) Telephone interview with Dr. David Sklaroff, Chairman of the Department of Radiation Therapy at Albert Einstein Medical Center, by Myrna Morganstern of HCCP, April 27, 1976, Philadelphia, Pa.
- (62) Telephone interviews with Dr. Mortimer B. Hermel, Chairman of the Jacob Gershon-Cohen Foundation, by Myrna Morganstern of HCCP, April 27, 1976, and August 16, 1976, Philadelphia, Pa. The Foundation was originated by Dr. Gershon-Cohen in the late 1950s to promote general medical education as well as radiological research. Funding for such projects came from Dr. Gershon-Cohen during his lifetime and has continued from private contributors since his death in 1971.
- (63) Interview with Dr. Robert L. Egan, Professor of Radiology and Chief of the Mammography Section at Emory University, by Myrna Morganstern of HCCP, April 30, 1976, Atlanta, Ga.
- (64) See note (62).
- (65) See note (62).
- (66) See note (25).
- (67) Gershon-Cohen, J., Berger, S.M., Delpino, L.: Mammography: Some remarks on techniques. Rad. Clin. N. Amer. 3:389-401, 1965, at 390.
- (68) Egan, R.L.: Experience with mammography in a tumor institution. Radiology 75:894-900, 1960.
- (69) See note (67).



- (70) See note (62).
- (71) Editorial. J.A.M.A. 177:1108, July 1, 1961.
- (72) Egan, R.L.: Letter to the editor. J.A.M.A. 178:440, October 28, 1961.
- (73) Gershon-Cohen, J.: Letter to the editor. J.A.M.A. 178:440, October 28, 1961.
- (74) See note (25).
- (75) Interview with Dr. Arthur Present, supervisor of the ACS-NCI Breast Cancer Detection Demonstration Project in Tucson, Arizona, by Devra Breslow of HCCP, May 1, 1976, Tucson, Ariz.
- (76) See note (63).
- (77) See note (25).
- (78) See note (25).
- (79) See note (24).
- (80) See note (25).
- (81) See note (25).
- (82) See note (75).
- (83) Gros, C.M.: Les Cancers Occultes du Sein et la de la Mamelle Tumorale. J. Rad. Electrol. 33:602, 1952.
- (84) Leborgne, R.: Diagnostico de los procesos patalogicos de la mama por la radiografia con la inyeccion de medios de contraste. Obstet. Gynecol. Lat. Amer. 2:551-561, 1944.
- (85) Lame, E.L., Pendergrass, E.P.: An addition to the technic of simple breast roentgenography. Radiology 48:266-268, 1947.
- (86) See note (11) at 6.
- (87) Haagensen, C.D.: Diseases of the Breast. Philadelphia, W.B. Saunders, 1956, at 127.
- (88) See note (63).
- (89) Egan, R.L.: Evolution of the team approach in breast cancer. Cancer 36: 1815-1822, 1975, at 1816.
- (90) See note (63).
- (91) See note (63).

- ( 92) See note (68).
- ( 93) See note (63).
- ( 94) See note (63).
- ( 95) See note (63).
- ( 96) Interview with Dr. Lewis Robbins, former Chief, Cancer Control Program,  
by Lester and Devra Breslow of HCCP, November 20, 1975, Indianapolis, Ind.
- ( 97) Log of Dr. Lewis Robbins, February 7, 1965.
- ( 98) See note (25).
- ( 99) See note (62).
- (100) See note (53).
- (101) See note (24).
- (102) See note (24).
- (103) See note (24).
- (104) Egan, R.L.: Radiographic Projections and Technical Factors. Chart  
published by the Eastman Kodak Company.
- (105) See note (72).
- (106) Remarks of S.M. Berger in Proceedings of the Sixth Annual Mammography  
Conference, April 19-21, 1967, ed. The American College of Radiology,  
pp. 67-69, at 67-68.
- (107) See note (106) at 67-69.
- (108) See note (96).
- (109) See note (96).
- (110) See note (96).
- (111) Robbins, L.C.: Purposes of the mammography reproducibility study. Cancer  
Bull. 14:102-104 at 104.
- (112) See note (89) at 1817.
- (113) See note (8) at 129.
- (114) See note (8).
- (115) See note (89) at 1820.

- (116) See note (8) at 127.
- (117) Interview with Dr. Luther L. Terry, former Surgeon-General of the United States, by Myrna Morganstern of HCCP, April 27, 1976, New York City.
- (118) See note (63).
- (119) Rogers, J.V., Powell, R.W., Egan, R.L.: Comparative mammography study. Am. J. Roentgenol., Rad. Ther., and Nuc. Med. 97:748-754, 1966.
- (120) See note (89) at 1818.
- (121) See note (63).
- (122) See note (89) at 1819.
- (123) See note (89) at 1818-1819.
- (124) Log of Dr. Lewis Robbins, August 30, 1964.
- (125) See note (124).
- (126) See note (89) at 1819.
- (127) Log of Dr. Lewis Robbins, February 7, 1965.
- (128) See note (127).
- (129) See note (127).
- (130) See note (75).
- (131) See note (75).
- (132) See note (75).
- (133) See note (75).
- (134) See note (75).
- (135) See note (75).
- (136) See note (75).
- (137) See note (52).
- (138) See note (24).
- (139) See note (24).
- (140) See note (24).

- (141) Strax, P., Venet, L., Shapiro, S.: Breast cancer found on repetitive examination in mass screening. Arch. Environ. Health 20:758-763, 1970.
- (142) Strax, P., Venet, L., Shapiro, S., et al: Changes in 5-year breast cancer mortality in a breast cancer screening program. In Proceedings of the Seventh National Cancer Conference, sponsored by the American Cancer Society and the National Cancer Institute, Sept. 27-29, 1972. J.B. Lippincott Co., Philadelphia, 1973, pp. 663-678.
- (143) See note (52).
- (144) See note (52).
- (145) See note (58).
- (146) See note (58).
- (147) Culliton, B.J.: Breast Cancer: second thoughts about routine mammography. Science 17:555-558, 1976, at 556.
- (148) See note (147).
- (149) See note (58).
- (150) See note (58).
- (151) Bailar, J.C., III: Mammography: contrary view. Ann. Int. Med. 84: 77-84, 1976.
- (152) See note (58).
- (153) See note (147) at 556.
- (154) Interview with Leon Ellwein, Ph.D., former member of the Diagnostic Research Advisory Group and member of the HCCP staff, by Myrna Morganstern of HCCP, August 24, 1976, Los Angeles, Ca.
- (155) See note (58).
- (156) See note (58).
- (157) A report to the profession from the Breast Cancer Task Force. Conn. Med. 39:166-169, 1975.
- (158) Vanselow, N.A.: Breast Cancer Demonstration Project. Ariz. Med. 32:30-31, 1975.
- (159) "Use of X-rays to Detect Breast Cancer Defended." Los Angeles Times, March 27, 1976, p. 16.
- (160) See note (58).



- (161) See note (58).
- (162) See note (151).
- (163) See note (58).
- (164) See note (75).
- (165) See note (75).
- (166) See note (75).
- (167) See note (58).
- (168) Report to Dr. Guy R. Newell, National Cancer Institute, by Dr. Lester Breslow for the Epidemiology-Statistics Task Force, July 15, 1976, at 5.
- (169) See note (168) at 6.
- (170) Wolfe, S.M., Warner, R.: Mammography: A Case for Informed Consent. A report of the Health Research Group, November, 1976.
- (171) See note (170) at 3.
- (172) Hermel, M.B., Murdock, M.G.: Microdose mammography. Accepted for future publication in Cancer. Article courtesy of Dr. Hermel.
- (173) See note (168) at 5 and note (170) at 6-7.
- (174) Strax, P.L., Malsky, S.J., Strax, N.: Millirad mammography in mass screening. Paper presented at the Third International Symposium on Detection and Prevention of Cancer, New York City, April 26- May 1, 1976.
- (175) Ruzicka, F., Kaufman, L., Shapiro, G., et al: Xeromammography and film mammography-comparative study. Radiology 85:260-269, 1965.
- (176) Wolfe, J.N.: Xerography of the breast. Radiology 91:231-240, 1968.
- (177) Wolfe, J.N.: Xerography of breast. Cancer 23:791-796, 1969.
- (178) Wolfe, J.N.: Mammography and xeroradiography. Mich. Med. 68: 37-38, 1969.
- (179) Egan, R.L.: Mammography, xeroradiography, and thermography. Clin. Obstet. & Gyn. 18:197-209, June, 1975.
- (180) See note (179) at 206.
- (181) Lawson, R.N.: Implications of surface temperatures in the diagnosis of breast cancer. Canad. Med. Assoc. J. 75:309-310, 1956.
- (182) Lloyd Williams, K., Lloyd Williams, F.J., Handley, R.S.: Infrared thermometry in diagnosis of breast disease. Lancet 2:1378-1381, 1961.

- (183) Wild, J.J.: The use of ultrasonic pulses for the measurement of biologic tissues and the detection of tissue density changes. Surgery 27:183-188, 1950.
- (184) Wild, J.J., Neal, D.: Use of high-frequency ultrasonic waves for detecting changes of texture in living tissues. Lancet 1:655-657, 1951.
- (185) Wild, J.J., Reid, J.M.: Further pilot echographic studies on the histologic structure of tumors of the living intact human breast. Am. J. Path. 28: 839-854, 1952.
- (186) See note (58).
- (187) Shapiro, S., Goldberg, J.D., Hutchison, G.B.: Lead time in breast cancer detection and implications for periodicity of screening. Am. J. Epidem. 100:357-366, 1974.
- (188) Shapiro, S.: Screening for early detection of cancer and heart disease. Bull. N.Y. Acad. Med. 51:80-95, January, 1975.
- (189) See note (188) at 93.
- (190) See note (188) at 93.
- (191) Shapiro, S., Goldberg, J., Venet, L., et al: Risk factors in breast cancer-a prospective study. In Host Environment Interactions in the Etiology of Cancer in Man. IARC Scientific Publication No. 7, Fogarty Int. Center Proc. No. 18, 1973, pp. 169-182.
- (192) See note (179) at 203-204.
- (193) Egan, R.L., Mosteller, R.C., Stevens, C.D., et al: High risk cancer patients. Unpublished paper contributed by Dr. Egan.

## CHAPTER 6

### THE DETECTION AND DIAGNOSIS OF LARGE BOWEL CANCER

#### Large Bowel Cancer - A Major Cancer Control Problem

Taken together, cancers of the colon and rectum continue to be the most common form of cancer in the United States. It is estimated that there were 99,000 new cases of cancer of the colorectum, or large bowel, in 1975. This represents nearly 15 percent of all new cancer cases. In the male and female population as a whole, colorectal cancer is a greater problem than lung cancer, breast cancer, or any other single cancer. (1)

There has been essentially no change in the combined incidence rate for this cancer over the past quarter century--although prior to this period there was a significant increase. (2) Even though the incidence of large bowel cancer has remained stable during the last 25 years, there has been a shift in the distribution from one site to another. Rectal cancer has declined while colon cancer has increased. This is illustrated in Table 1.

The age-adjusted incidence of cancer of the rectum has dropped from nearly 17 per 100,000 population down to just a little over 12. However, colon cancer has increased enough to essentially offset this entire reduction. It has been suggested that part of the reason for these opposite trends between colon and rectum cancer is due to inconsistencies

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Table 1: Age-Adjusted Incidence Rates per 100,000 Population

	Colon			Rectum		
	1947-48	1969-71	Change (%)	1947-48	1969-71	Change (%)
White Male	23.8	29.0	21.8	20.7	16.0	-22.7
White Female	26.0	24.8	-4.6	13.9	9.6	-30.9
Non-White Male	13.7	22.9	67.2	11.4	13.0	14.0
Non-White Female	11.9	23.6	98.3	12.3	7.6	-38.2
Total	23.8	26.4	10.9	16.6	12.2	-26.5

Source: NCI unpublished data: based on seven metropolitan areas in the second and third National Cancer Surveys and adjusted to the age distribution of the United States population in 1950.



over time in the classification of tumors near the rectosigmoid junction as either colon or rectum cancer. However, a study of this question concluded that the reported differential incidence trends were not due to changes in the assignment of cancers in the rectosigmoid part of the intestinal tract. (3)

During the 1947-71 period, the incidence of colon cancer in white males has increased by almost 22 percent, while the incidence in white women has actually dropped slightly. In both black males and females, the incidence of colon cancer--once half that among whites--is increasing to the point where it has almost reached that of the white population.

Control of large bowel cancer through early diagnosis and treatment has not been accelerated to any appreciable extent during the past quarter century. Five-year relative survival rates have changed little since the 1950s, although between the 1940s and 1950s there was a marked improvement which paralleled the improvement in almost all cancer therapy during this earlier period. (4) This is shown in Table 2.

Table 2: Five-Year Relative Survival Rates (%)\*

	Period of Diagnosis			
	<u>1940-49</u>	<u>1950-59</u>	<u>1960-64</u>	<u>1965-69</u>
Colon	32	44	44	45
Rectum	29	40	37	41

\* Based on data for white patients

Source: Cutler, S.J., Myers, M.H., and Green, S. (5)

Part of this general improvement in therapeutic outcome during the 1940s was undoubtedly due to such factors as improvements in anesthesia, the control of postoperative infections, and other advances in patient monitoring and support. These advances decreased operative mortality and also enabled a greater number of patients to be treated surgically. Another factor contributing to this improvement in survival was earlier diagnosis of the disease. Table 3 illustrates this increase in the percent of patients diagnosed with localized disease during the 1940s and early 1950s. Also shown is the percent of patients treated surgically. Although modest, this initial trend in improved diagnoses did not continue and, since the mid-1950s, the proportion of patients with localized disease at diagnosis has evidenced no significant change.

Table 3: Percent of Patients with Localized Disease at Diagnosis and Percent Treated Surgically

	1940-49		1950-54		1955-64		1965-69	
	<u>Loc.</u>	<u>Surg.</u>	<u>Loc.</u>	<u>Surg.</u>	<u>Loc.</u>	<u>Surg.</u>	<u>Loc.</u>	<u>Surg.</u>
Colon	36	58	38	76	41	81	42	84
Rectum	37	55	42	72	45	76	46	78

Source: Levin, D.L., Devesa, S.S., Godwin, Jr., J.D., et al (6)

With little change in overall colorectal cancer incidence and no appreciable change in survival rates during the most recent 25 years, there is little basis upon which a significant change in mortality could have become manifest during this same time period. In fact, during the past quarter century, the combined death rate from colon and rectum cancer has

not changed to any great extent. Fortunately, the general trend is at least downward--from about 22 per 100,000 U.S. population in 1950 to about 19 in 1973. (7)

### Means of Control

Have sufficient advances been made so that the control of large bowel cancer can now be accelerated by improving performance in prevention, early detection, diagnosis, or treatment? The future does hold promise. In particular, developments affecting detection and diagnosis hold the potential to make a marked impact upon survival rates. This potential for impact is supported by the fact that for large bowel cancer diagnosed in a localized stage--confined to the colon or rectum without lymph node involvement--the five-year survival is about 70 percent, or double that of patients whose cancer is first diagnosed after it has spread beyond the site of origin. (8) The other areas of control seem to hold less immediate promise.

It is generally acknowledged that there is little programmatic control activity currently under way to bring about a decreased incidence of large bowel cancer by utilizing primary preventive measures. The problem is that there are no generally accepted primary prevention measures available specifically for large bowel cancer. This area continues to be an active one for epidemiological research, however. For example, some investigators have, on the basis of international differences in risk of colorectal cancer, implicated diet as an influence. Differences in diet are significant, particularly in the proportion of unabsorbable fiber present; and as Dr. Burkitt of London notes, "removal of dietary

fiber may be a causative factor." (9) Low-fiber Western diets typically are high in animal fat. It has been conjectured that diets with this composition are associated with increased intestinal bacteria that may lead to the intraluminal production of carcinogenic compounds and, with high levels of fecal bile acid, metabolites that may result in carcinogenic activity. (10,11,12) It is epidemiological research such as this that has given rise to speculation linking the highly refined Western diet, rich in starches and deficient in bulk, with the elevated risks for bowel cancer in North America and Western Europe. (13) While present findings are not conclusive, they do provide leads for planning further research on diet and cancer.

Although these findings suggest a promising means for control in the future, there is no generally accepted basis for primary prevention available today. The cancer control developments affecting colorectal cancer, as noted earlier, are centered in the secondary sphere, involving the detection and removal of lesions that may be precursors of cancer and, frequently, the detection and diagnosis of cancer itself. Further along the cancer control spectrum--in the treatment realm--no new developments with significantly improved effectiveness have occurred in the past quarter century. However, current research efforts, particularly in new multimodality treatment regimens, provide some hope for future improvements in this area as well.

How is cancer of the large bowel diagnosed? As with other cancers, diagnosis is based on being able to detect an abnormality and then examining it microscopically to determine whether it is cancerous. But the detection of an abnormality in the large bowel poses some unique



difficulties because of its sheer size and relative inaccessibility. Current practice offers various means to examine this organ macroscopically for the possibility of cancer. This includes physical examination, chemical testing, and both indirect and direct visualization. Physical examination entails palpation of the rectum--the digital rectal. Chemical testing seeks to identify fecal occult blood which is the result of a bleeding abnormality. The standard means of indirect visualization is the barium enema, an X-ray of the large bowel with contrast material. (Among the more experimental means of indirect visualization is ultrasonic echography.) Direct visualization is achieved through endoscopic examination of the rectum and sigmoid by the proctosigmoidoscope; and examination of the descending, transverse, and ascending colon by the colonoscope. Once an abnormal area is detected, a tissue biopsy is taken using the sigmoidoscope or colonoscope; microscopic examination of the specimen (and, in some instances, cytologic examination of feces, colonic washings, or endoscope-obtained brush smears) then either confirms or rejects any suspicion of cancer. (14,15,16)

Some claim that by using this battery of tests in a meaningful sequence, the detection of colorectal cancer in an early stage can now be achieved. (17,18) Despite this enthusiasm, the lessons learned from cervical cytology indicate that the widespread application of even a single, relatively simple test cannot be taken for granted. Moreover, the cost-effective application of current techniques to the screening of asymptomatic populations for colorectal cancer has yet to be demonstrated.

The battery of detection and diagnostic tests includes two that are relatively recent additions: the test for fecal occult blood; and colonoscopy.

The chemical testing of stools for occult blood is not a new idea, but the practical application of this concept in screening is a recent development. Much of the present-day potential for control of colorectal cancer through screening rests with this technique. Colonoscopy, or more generally fiberoptic endoscopy, is a technological development that did not exist before the 1960s. It represents a major contribution to the diagnosis of colorectal cancer. Each of these two developments will be discussed in greater detail and the events which influenced their development and application traced.

#### Test for Occult Blood: Historical Development

Apart from emerging epidemiological clues--and their implications for preventive policies--an important technique for early detection of large bowel cancer has been developed on the basis of a chemical test for blood in the stool. This test depends on the property of hemoglobin or its derivatives to aid the oxidation of chromogenic compounds, such as benzidine, orthotolidine, and guaiac, by hydrogen peroxide. A positive reaction between the active chromogenic agent and a stool specimen is an indication of the presence of occult blood. The significance of this is that colorectal cancers are known to result in gastrointestinal bleeding.

Translation of this knowledge into a potential for screening has been evolutionary and any significant degree of success is only a recent development. In fact, as recently as 1960, a report on the role of fecal chemistry in cancer detection concluded with the following discouraging comment:

If sigmoidoscopies had been performed only on patients with stool specimens positive for blood, the number performed would have been cut 90 percent, and one-third of the carcinomas, as well as most of the benign and malignant polyps, would not have been found. Presently, then, this test for fecal blood is not acceptable for selecting asymptomatic patients for sigmoidoscopy. (19)

What are the historical events in the evolution of this test?

It is reported that "chemical reactions for occult blood in the feces in disorders of the alimentary tract" first received attention in Germany in 1901 and that the first English publication was in 1907. (20) By the 1920s, a considerable amount of experimentation, using various chemicals, had been carried out to determine the value of this test as a diagnostic aid and as a means to monitor the effect of therapy, for example, on bleeding gastric and duodenal ulcers. (21)

Apparently, throughout this period, conclusive results were not forthcoming, as expressed by Bell in 1923:

There is an increasing likelihood that ultimately no reliance will be placed upon this diagnostic and therapeutic aid. The variety of tests which have been advocated and the numerous modifications in their technique contribute largely to this unsatisfactory position....At present probably every biochemical laboratory has its own routine method of performing this examination... (22)

Bell investigated spectroscopic examination and three chemical tests (benzidine, guaiacum, and phenolphthalein) in hospital patients who had disease of the alimentary system and others who presumably had no gastrointestinal tract disorder. In taking cognizance of the situation at the time, he stated that "the danger of adding still further to the confusion by another contribution to the copious literature is not to be ignored." (23) Ogilvie, a British investigator, noted the same divergence of opinion in a study of what he called "alleged fallacies." (24)



The purpose of his study was to bring "the examination of the stools for occult blood within the scope of the busiest general practice equally with the examination of the urine for albumin and sugar." (25) The "fallacies" that he studied included primarily the effect of diet (at least one observer was of the opinion that diet had no effect). Other "fallacies" which he reviewed included concerns about bleeding from the gums, the use of hand toothbrushes, sucking of teeth, and iron medicines.

As illustrated by these references, the issues surrounding the quantitative sensitivity to occult blood of the various tests, the selectivity of the tests, and the elucidation of factors affecting this were not resolved during this time period. Furthermore, the next logical investigative step--determination of the actual diagnostic efficacy of testing for occult blood--seemed to get little or no attention. In fact, after a survey of the literature, Hoerr and his associates at the Ohio State University Hospital Department of Surgery noted as late as 1949 that investigative work was directed primarily toward sensitivity (the same issues raised above) and that:

[L]iterature concerning actual clinical utility of the tests is sparse....[W]e were unable to find a single study evaluating the usefulness of such a test as an adjunct to a complete diagnostic work-up of a patient, comparable to the universally employed blood count and urinalysis (26)

Their investigations were conducted using three reagents (benzidine, orthotolidine and guaiac) in unselected hospital patients, none of whom were placed on a special diet because, as they noted:

It has been emphasized by many writers that it is desirable to place the patient on a meat-free diet for several days before the stool is tested in order to avoid false positive reaction occult blood from



ingested food. It was concluded at the outset of this study that such preliminary dieting was out of the question if the test were to be used widely without specific indications. In this study, no patients had any dietary restrictions not imposed by the nature of their illness, and stools were taken as they came. (27)

They concluded that benzidine and orthotolidine were too sensitive to be used for routine testing without a meat-free diet but that the guaiac test was appropriate for screening, and they planned to utilize the test on dispensary and office patients. (28) Support for the conclusion regarding benzidine was provided in a discussion of their presentation by Dr. Berk:

One problem that arose in the recent war [World War II] was the loss of man-hours due to prolonged hospitalization of military personnel. It was found that an important cause of this was a positive reaction for occult blood on examination of feces. This observation led to hospitalization and protracted diagnostic studies in search of a lesion responsible for the occult blood indicated by the positive result. When it was pointed out that the unmodified benzidine test, which was the one usually employed, was extremely sensitive and when a less sensitive test was substituted, the loss of man-hours was reduced. (29)

Actually, this recognition of the greater sensitivity of benzidine was not new; it was recognized even as early as the 1920s. (30,31)

As time went on, firm evidence supporting the efficacy of these tests in diagnosis was still lacking:

In spite of the reliance placed by many clinicians upon the testing of the feces for occult blood as an adjunctive or even a required part of the physical examination, there is little published scientific fact to justify the faith with which these tests are performed. (32)

However, in other respects the findings appeared to be moving toward clarification:

Certain other facts have already been established which aid in the understanding and optimal use of tests for fecal blood by various reagents. The variety of reagents available includes those which are suitable for screening purposes (e.g., gum guaiac), as contrasted with more sensitive reagents for estimating the amount of blood present (e.g., benzidine, orthotolidine, and the Gregersen reagent composed of benzidine and barium peroxide). (33)

#### Early Detection: Occult Blood Test

After several decades of experimentation and publications, primarily on the sensitivity issue, some attention was finally turned toward evaluating the contribution of some of these tests in detecting colorectal cancer. One of the first evaluations was carried out by Cameron and Thabet from the Ohio State University Hospital Department of Surgery, using a benzidine reagent with a test adjusted for its sensitivity to small amounts of fecal blood (34) Their results were reported in 1960. As was noted earlier, their findings did not suggest a favorable outlook for fecal chemistry in screening. These negative results surely did not generate enthusiasm for the occult blood test. However, the concept of an accurate test for fecal occult blood was apparently appealing enough so that study of it continued, and in 1967 a favorable report was presented by David Greigor, also at Ohio State University. (35) He reported that:

In a survey of 2,000 physical examinations performed in an internist's office, seven patients with invasive carcinoma of the colon were found. None of the patients in the survey were examined because of large-bowel symptoms. All seven patients had positive tests for occult blood in at least one of three stool specimens. (36)

The primary difference between this and the 1960 study was the methodology for specimen collection (neither one specified a meat-free or

other special diet). Instead of a single fecal specimen, Greegor asked each patient to submit a specimen from more than one portion of three separate evacuations. Aesthetically, the testing of several three- or four-day-old stools presented problems. To make this multiple stool procedure more agreeable to patient, technician and physician, a manufacturer was requested to make special guaiac-impregnated test slides that could be prepared by the patient and mailed in for testing. (37) Although benzidine was chosen over guaiac as the active chromogenic agent in the earlier study, it should be noted that its use has since given way to orthotolidine (Hematest) and guaiac (Hemoccult test)--very likely because of the proven carcinogenic properties of benzidine. The guaiac-impregnated paper slide (Hemoccult) used by Greegor is generally judged now to be the preferred material for fecal occult blood testing. (38,39) The impregnated slide overcomes the traditional problems associated with the guaiac test, namely, poor quality control of guaiac solutions and deterioration of the reagent. (40,41)

Greegor's first study overcame the problem of false negatives, but he subsequently realized that without a special diet the number of false positives would be excessive.

In 6 months, 128 patients were tested [those positive on at least one guaiac test] and two cancers detected. Twenty-three percent of the patients were guaiac-positive, which meant that almost 1 out of every 4 routine physical examinees was subjected to the cost and discomfort of a barium enema. While this requirement was not impossible to meet, it was made more unacceptable by the fact that over one-half of those having x-ray showed no colon abnormalities whatsoever.

We took the obvious step and required a meat-free diet during preparation of stool slides. Since a bland diet will often pacify an early bleeding condition, we requested that the diet be high on residue. (42)



The result of this modification was that in a subsequent study of 900 patients only five percent were guaiac-positive and thus examined further. The five percent then divided as follows: one percent were proved to have asymptomatic cancer, two percent had diverticulosis, one percent had non-malignant polyps and the remaining one percent were judged to be false-positives. (43)

In utilizing the chemical test for the detection of occult blood, it is now clear that the test must be used in a specifically prescribed fashion if the false negative and false positive reactions are to be minimized. Attention must be given to both diet (to reduce the number of false positives) and multiple testing (to reduce the number of false negatives). According to one observer: "The test for occult blood in a random stool on an unmodified diet is worthless." (44) The method of specimen collection generally followed is the one recommended by Greigor. (45) He recommends that the test be used in conjunction with a special four-day, no meat, high residue diet (the residue or bulk reduces the false negatives) during which time hemoccult slides are prepared from daily bowel movements on the second, third, and fourth days. Greigor believes that with only a single stool specimen (a continually attractive proposition because the specimen could be taken in a physician's office) the false negative rate will be excessive, rendering the test of little practical value.

Repeated testing over more than one day will reduce the possibility of missing a colorectal cancer that, for example, may bleed only intermittently. The special meat-free diet plays its role by reducing the number of false positive reactions. This was illustrated in a recent American Cancer Society-supported mass screening program carried out in



Mercer County, New Jersey by the local medical society. (46) They found that positive reactions from an "on the spot" specimen taken without a special diet were confirmed only 11 percent of the time by a positive reaction for blood in one or more of the three specimens taken while on a special diet.

As in all mass screening, follow-up of positive findings is critical. In the Mercer County, New Jersey screening program, follow-up evaluation of individuals with a positive test result was difficult to achieve; after spending a significant amount of effort to encourage follow-up and to monitor the results, adequate follow-up was achieved for less than one-third of those with positive test results. (47)

It is clear that further investigations are necessary to determine the proper application and technical effectiveness of the stool guaiac test in mass screening. Indeed, further study is currently in progress. Perhaps the most extensive study of efficacy in an asymptomatic population is the one being carried out at the Memorial Sloan-Kettering Cancer Center under partial support from the NCI through the National Large Bowel Cancer Project. (48) At the same time, the American Cancer Society is active in encouraging the investigation of screening under the guidance of its Colon Cancer Committee.

Cost considerations are also beginning to receive attention and, as a result, a new variable is being added to the analysis. For example, in a recent look at cost effectiveness, it was suggested that the marginal benefit to be gained from the last stool guaiac test in Greegor's series of six is not worth the effort or cost to collect it. (49)

Although more widespread evaluation is needed, at the present time a test for fecal occult blood represents the most attractive means for

mass screening of asymptomatic populations. There is little doubt that the potential application of the test on a mass screening basis will continue to receive considerable attention and close scrutiny. Thus, the question is not whether further investigation will take place, but whether it will be piecemeal, and in many respects haphazard, or systematic with carefully designed, definitive studies. What appears to be happening with the application and evaluation of the stool guaiac test as a screening tool is a repetition of the experience with the Papanicolaou test--sporadic studies with little central planning or forceful leadership from any nationwide institution or professional group. Is it time to evaluate the stool guaiac test in a randomized clinical trial? Are the test and follow-up procedures good enough to permit long-term evaluation, including impact on mortality? As is the case with the Papanicolaou test today, there may come a time, perhaps in the not too distant future, when for ethical reasons it will not be possible to test effectiveness in a controlled prospective study.

#### GI Endoscopy: Early History

The history of gastrointestinal endoscopy from its primitive and frustrating beginnings to its present state of sophistication has been slow largely because it had to await developments in light sources, light transmission, optics and photography. However, many ingenious devices were used with limited success in the earlier period which laid the foundation of gastrointestinal endoscopy.

The history of gastrointestinal endoscopy may be looked upon as having developed through three phases: the earliest phase from 1795 to 1932 when the straight rigid tubes were used, the second phase of semi-flexible tube endoscopy from 1932 to 1958 and finally the present era of fiberoptic endoscopy, which has continued at a very rapid pace since 1958. (50)

This introductory statement appears in a recent text on gastrointestinal pan-endoscopy with contributions from around the world, edited by Leonard H. Berry.

The development of the first illuminated endoscope, in 1795, for examination of the rectum and uterus, is credited by some to P. Bozzini of Germany. He used a candle as a light source. A subsequent milestone in illumination was provided by A. J. Desormeaux who, in 1853, used a lamp that burned a mixture of alcohol and turpentine to provide light that, after going through a lens system, was reflected into the endoscope by a forehead mirror. During the latter part of the nineteenth century, most of the attention in instrument development appears to have been directed toward gastroscopes, esophagoscopes, and cystoscopes. (51)

By the turn of the century, several further attempts were made to improve upon instrumentation of examination of the rectum. The work of Howard A. Kelly of Baltimore, beginning in 1895, is identified as laying the foundation for the modern era of proctosigmoidoscopy. Kelly introduced "straight metal tubes of different calibers and lengths." Developments shortly thereafter by Kelly and others resulted in the replacement of reflected light by electric light illumination at first the distal end and then the proximal end of the endoscope. (52)

The second phase of GI endoscopy development was directed toward the upper GI tract and began when rigid gastroscopes gave way to semi-flexible lens scopes. In 1932, R. Schindler introduced a semi-flexible gastroscope which was based on the principle that an image could be transmitted through a curved tube with a series of short-focal distance lenses. This development was the beginning of the modern era of gastroscopy. (53)



For the first time, there was a real practical breakthrough which made perhaps four-fifths or seven-eighths of the gastric mucosa adequately illuminated and excellently visualized. (54)

Attention continued to be focused on upper GI endoscopy and numerous modifications were made in the Schindler-type gastroscope. (55) For example, one advance was the development of an improved rigid rod lens system by Professor Harold Hopkins which increased light transmission by a factor of nine. (56) Photography, utilizing both extragastric and intragastric cameras, was also being attempted. Intragastric cameras were of interest as a means to inspect the part of the stomach not directly visible by gastroscopes in use at the time. (57)

The Japanese, in applying their miniaturization and photographic technology to endoscopy, are credited with the first practical development of an intragastric camera in 1950. (58) The gastro camera became very popular in Japan, a country with a relatively high incidence of stomach cancer, and color photographs of remarkable brilliance were being obtained. (59) Attempts to apply techniques of flexible endoscopy to the colon were reported by Matsunaga and others with the use of the sigmoid camera--a modification of the gastro camera. (60) Because of difficulties inherent in blind insertion and blind aiming of photography, use of intragastric cameras was discontinued after flexible endoscopes incorporating fiberoptics were introduced.

Although great strides were being taken in instrumentation for gastric diagnosis during the 1930s, 1940s, and 1950s, little notable development appears to have been made in lower GI endoscopy during this period. (61,62) Nevertheless, this period of technologic development provided a scientific foundation upon which all of GI endoscopy would



advance during the next two decades. As stated by Henning and Berry:

The Schindler era of gastroscopy--brilliant in its day--was a period of search for the final perfection of a new and dramatic breakthrough in gastric diagnosis. In relation to modern industrial expertise, the required quarter of a century of semi-flexible gastroscopy was not much faster than the crude and painful preceding century of frustrations. There had to be a time of education of gastroenterologists, surgeons and patients. There had to be a time of establishment of the value of the method in a technically advanced society. The Schindler era served these purposes and in the process, a massive body of scientific literature in clinical gastroenterology was also established. Thus, a new diagnostic clinical science supported by new concepts was ready to encompass the next major breakthrough, namely the current era of Fiberoptic Gastrointestinal Endoscopy. (63)

#### Fiberoptic Endoscopy: Historical Development

The fiberoptic era of endoscopy began with the development of a fiberoptic gastroscope by Hirschowitz and his co-workers at the University of Michigan in 1958. (64) This new instrument created great interest, and progress in instrument development over the subsequent years was rapid. (65,66) The development of fiberoptics and its introduction into medicine revolutionized all of endoscopy, but particularly gastrointestinal endoscopy. What were the events that brought about this epic period? What is fiberoptics?

Fiberoptics is a branch of optics that uses bundles of transparent fibers (glass or even plastic), each with a thread-like diameter, to transmit light. Light is transmitted from one end to another no matter how the bundle is curved. The principle of transmitting light along curves is not new. The basic laws of physics governing the phenomenon of light refraction and reflection were described during the seventeenth century by

Christiaan Huygens. A demonstration of transmitting light along curves took place in 1870 by John Tyndall using a curving jet of water. Recognition that light can be sent through a hollow curved pipe of polished metal is also old. However, because of loss of light during reflection, hollow light tubes did not find any practical application. When exceedingly thin glass fibers are used, little loss of light results. A single fiber cannot transmit an image but only a certain intensity of light. An image is composed of light of varying intensity being reflected from different areas of the object. When the geometric relationship of the fibers at both ends of the bundle are made identical (a coherent bundle), an entire image can be transmitted with little distortion. Each fiber transmits, at a particular light intensity, a very small segment of the image. (67,68)

The first practical application of conveying images through glass fibers was described by Logie Baird in a British patent specification in 1928. (69)

He was able to transmit optical images through such bundles and project them via a lens onto a suitable screen...the light transmission of these early fibre bundles was however so poor that there was no possibility of employing them for transmitting light into the bowel, let alone back to the eyepiece. (70)

Apparently, the first successful construction of a fiberscope was accomplished by two physicists, H. H. Hopkins (the developer of the previously mentioned Hopkins lens system) and N. S. Kapany. They also recognized the potential of the fiberscope in medical endoscopy and reported their work in January, 1954:

An optical unit has been devised which will convey optical images along a flexible axis. The unit comprises a bundle of fibres of glass, or other transparent material, and it therefore appears appropriate to introduce the term "fibrescope" to denote it. An obvious

use of the unit is to replace the train of lenses employed in conventional endoscopes. The existing instruments of this kind, for example, cystoscopes, gastroscopes and bronchoscopes, etc., consist of a train of copying lenses and intermediate field lenses. They are either rigid or have only limited flexibility. Moreover, the image quality of these systems is poor, since they consist only of positive lenses which give rise to a very large curvature of field. In existing gastroscopes, the total number of lenses employed may be as many as fifty, and in consequence the light transmission is poor, due to the total glass path and the number of air-glass surfaces, in spite of blooming. Even more important in this respect, however, is the need to use small relative apertures for such instruments, this being necessary if acceptable definition is to be obtained with such large field curvature. (71)

Fiberoptics offered the combination of flexibility and image transmission without the need for prisms or lenses. However, loss of light because of less than total internal reflection during transmission was a major problem:

This problem of loss of light was a very real one during the period 1954-1958 when much of the fundamental research on fibre-optic light transmission was being performed by Hopkins' group at the University of Reading and Lawrence Curtiss at the University of Michigan.

A practical solution to this problem was found by Curtiss at the end of 1956 when he drew glass-coated fibres from an assembly of high index glass within a low index glass tube....A 3-ft. long image bundle constructed from these fibres showed high transmittance, a half angle of  $40^{\circ}$ , and excellent image contrast. This construction became the basis of the first clinically useful fully-flexible gastroscope. (72)

The events leading to the involvement of the University of Michigan in this work have been recounted by Dr. Bergein Overholt (who became involved in the development of fiberoptic endoscopes suitable for examination of the colon):

The application of fiberoptics to endoscopic instruments dates back to 1954 when Timothy Counihan, then a resident in internal medicine at the Postgraduate Medical School of London, brought to the attention of Dr. Keith Henley an



article in Nature that first described flexible fiber-optics. The application to gastrointestinal endoscopy was apparent to these men. Eventually Dr. Henley passed the idea to Dr. Basil Hirschowitz and Dr. H. M. Pollard. Dr. Pollard in turn contacted Professor Barker, then Chairman of the Department of Optical Physics in the School of Engineering, University of Michigan. With Professor Barker's interest in the subject, he designated a member of his department, Professor C. W. Peters, to consider the project. With Professor Peters, Dr. Hirschowitz, and Dr. Pollard, they initiated the development of glass fibers, with the student aid of Mr. L. E. Curtiss. Together this group designed and developed the fibergastroscope which was first used in February, 1959 at the University Hospital, University of Michigan. (73)

In a recent interview, Dr. Pollard noted that he offered a job to Kapany but that he took a Canadian offer instead and so Peters, at the University of Michigan, was assigned to work with Pollard and Hirschowitz. (74)

The first application of fiberoptics to lower GI endoscopy was in providing improved illumination, rather than image transmission. Fiberoptics was incorporated with the rigid sigmoidoscope as a means of providing an improved source of both proximal and distal lighting. (75,76) The resultant early benefits are noted by Robert Turell, who was active in these early developmental efforts:

Such intense illumination, while in excess of requirements under ideal circumstances, is of substantial clinical benefit when light carriers are dimmed by blood, mucus or feces....Furthermore, the fiber optics provide not only a superior but also a cold light. Thus, the annoyance and interruption of the examination caused by overheating and burning out of bulbs during performance of endoscopy are totally eliminated. (77)

Development of a flexible sigmoidoscope utilizing fiberoptics for both the light source and image transmission began in 1960 and 1961 with the work of Turell in New York City and Bergein Overholt, a resident under Pollard, in Ann Arbor, Michigan. (78,79) Similar work was initiated



shortly thereafter in Japan. (80) Technical problems with the design and development of such an instrument were evidently substantial. Dr. Turell was reporting difficulties associated with the contents of the large bowel and in directing insertion as late as 1969:

At the present time, the flexible fiber optic colonoscope previously described is undergoing extensive studies and, unlike the rigid sigmoidoscope, is not yet ready for general or routine clinical use.

To date my work with the colonoscope has yet to bear clinical fruits. In fact, I am quite disappointed on several fronts, namely, the time it takes to intubate with the patient weakening in the process, my inability to obtain a perfectly empty colon regardless of the preparation and, finally, the size of the specimen obtained with the tiny biopsy forceps. (81)

Reflecting back, Wolff and Shinya recently commented on an earlier report by Turell: (82)

Early incorporation into a flexible sigmoidoscope resulted in a bumbling attempt at clinical application, the unfavorable reports which probably contributed to delays in this area while rapid advances were going on in fiberoptic investigation of the opposite end of the alimentary tract. (83)

Success with a flexible instrument, when it finally did come in the United States, was reported by Overholt in 1967 and 1968. (84,85) Overholt utilized a new 50 cm flexible fiberoptic sigmoidoscope that was developed with the Eden Instrument Company and the Illinois Institute of Technology Research Institute. (86,87) The Cancer Control Program of the United States Public Health Service was also assisting Dr. Overholt in "working with various groups around the country on this instrument." (88) However, as Dr. Pollard recalls, the federal Cancer Control Program was interested but not willing to provide direct support for instrument development, the reason that they were contacted for

assistance in the first place. (89) (See Book Two, Chapter for a different view of the role of the federal Cancer Control Program, as recalled by Dr. Lewis Robbins.) Early support for instrument development was provided to the University of Michigan by a private donor. (90)

As success was being realized, the development of instrumentation progressed to increasingly longer fiberscopes. Within a short time, visualization of the entire large intestine including the descending colon, transverse colon, ascending colon and cecum (a length of about six feet) was achieved with the colonoscope.

Success was also being achieved with the flexible gastroscope. Today, using a single instrument, examination of the esophagus, stomach, and duodenum can be performed safely on a large scale by well-trained gastroenterologists or surgeons and with minimal patient discomfort. (91,92) These new fiberoptic instruments permit direction control of the viewing lens for detailed inspection of lesions. They also contain open channels through which instrumentation for the collection of tissue and fluids can be introduced and certain therapeutic techniques carried out. Serial examinations or follow-up studies, which previously met with patient resistance, can now be undertaken.

As is evident, most of the developmental work in lower GI endoscopy has been done within the last decade, but the state-of-the-art has already reached such an advanced stage that direct visualization of the entire gastrointestinal tract is now possible. This was illustrated in a recent paper by Shinya and Wolff where a photograph was reproduced showing simultaneously a small bowel endoscope which has reached the cecum through the upper GI tract and a colonoscope that has reached the cecum from below.

They noted, "in this way, both scope tips have met from above and below and visualized the entire gastrointestinal tract." (93) Further technological advancement in instrumentation and experience in technique can be expected to accelerate the already rapid evolution which has taken place.

#### Colonoscopy: Application

The merits of colonoscopy lie in its use as a diagnostic and therapeutic tool. It clearly is not intended for use in a screening mode. Colonoscopy is an important new procedure in the orderly diagnostic investigation of a patient with an already detected colorectal related abnormality. It provides an important complement to the barium enema in determining the site and extent of the cancer or other abnormality. Its effectiveness has been firmly established, and recent experience substantiates the view that it is as valuable, or even more valuable, than any other single diagnostic tool, including diagnostic radiology, in the diagnosis of colorectal cancer. (94)

Furthermore, the procedure is not limited because of the need for extensive prior medication. General anesthesia is rarely used or even considered since the recognition of pain by the patient serves as a warning to the endoscopist. Sedation induced by various analgesic agents is the only medication used routinely to minimize patient discomfort and anxiety. (95,96)

Its use is being extended into therapeutic areas, for example in the removal of polypoid lesions beyond the reach of the rigid sigmoidoscope. With the colonoscope, polyps or tumors protruding into the intestinal lumen, from the rectum to the cecum can be identified, biopsied and frequently removed.



The application of colonoscopy to diagnostic investigations and to patient management is particularly significant in helping to better understand the role of certain polyps as potential precursors in the natural history of carcinoma of the colon and rectum. This is important because a continuing controversy surrounds the question of whether an adenomatous polyp, a relatively common and removable benign polypoid lesion, can become transformed into invasive and metastasizing carcinoma of the colorectum. The importance of this is underscored by the fact that polypoid lesions are reported to occur in anywhere from four to 12 percent of all persons undergoing proctosigmoidoscopy, with the majority of these being categorized as benign at the time of morphologic examination. (97) The prevalence of adenomatous polyps as determined by a more complete and careful inspection of the entire large bowel in autopsy cases shows great variation and was reported to be as high as 50 percent in one series. (98)

In a frequently referenced study by Spratt and Ackerman, published in 1958, the previously held belief that adenomatous polyps of the colon and rectum were an early precancerous forerunner in the development of frank cancer was disputed. (99) Their proposition was that "the most lethal variant of colonic and rectal cancers begins as an infiltrating malignant ulcer similar to the malignant ulcer...[seen on] other epithelial surfaces rather than as polypoid growths." (100) Although the school of thought that colorectal adenomas are not premalignant and do not undergo transformation into invasive cancer gained acceptance in many circles, (101) challenges to this view continue to be offered. (102,103,104) The issue is undoubtedly clouded by differences in terminology and pathologic



descriptions of the various polypoid lesions that fall along the histologic spectrum of neoplastic change. For example, for a specific but uncommon type of adenomatous polyp, called a villous or papillary adenoma, there appears to be general agreement that this neoplastic lesion is a potential forerunner to cancer and that, in some instances, it may even be malignant at its inception. (105,106) Familial adenomatous polyps (histologically the same as other adenomatous polyps) are hereditary lesions and even more uncommon, but these polyps, which occur at a relatively young age, eventually progress to invasive cancer in all cases and thus there is general agreement on the need for definitive treatment. (107,108)

It is clear that an understanding of the role of polypoid lesions in the natural history of large bowel cancer has many gaps. The risk of colorectal cancer in patients with the relatively common adenomatous polyp must await further evidence and study. Those who view most polyps as being potential precursors of carcinoma consider the detection and removal of these lesions of great significance for cancer control. (109) Since morphologic examination and the ruling out of the possibility of invasive cancer is best done when the complete lesion is removed during biopsy, it is suggested that even benign appearing polyps be totally removed when the risk of the therapeutic procedure is low. (110,111) In the past, a problem arose when a grossly benign appearing polyp was found through radiography. In this case laparotomy was the only available means to examine further a lesion that was very likely a benign adenoma but beyond the reach of biopsy with the conventional 25-cm rigid sigmoidoscope. The question of whether adenomatous polyps had the potential

to transform into invasive cancer, and the associated rate of transformation and growth, was at the center of the patient management decision. Fortunately, today, it is possible to biopsy and remove polyps from all parts of the colon by endoscopic means. (112) The result is a dramatic reduction in possible complications and a circumvention of the hospitalization associated with a transabdominal polypectomy. (113)

The relative safety and effectiveness of colonoscopy in the hands of an expert has been demonstrated, although training and experience are essential in order to realize its full potential. (114,115) The GI endoscopist needs to receive training in instrumentation, techniques of manipulation, interpretation of findings (gained primarily through experience), and in recognizing the indications as well as potential hazards of colonoscopy.

It is important to note that the success that has been reported with colonoscopy, with little or no adverse effect on the patient, has been the experience of investigators with adequate training and prior experience. It is probably not realistic to expect this same degree of achievement from those new to colonoscopy. Colonoscopy is an inherently difficult and potentially dangerous procedure. Thus, a certain amount of caution is necessary to ensure an orderly expansion of its use and to limit the procedure to those with the requisite training. This problem was discussed by Dr. Margaret Sloan of the National Cancer Institute's Division of Cancer Control in a recent interview.

Anybody who has the money can go out and buy a flexible colonoscope. All kinds of doctors without any training at all are going out and doing this sort of thing, particularly those who don't even know what a normal colon looks like, because they can charge a lot of money for doing the examination, whether they can do it well or not. (116)

Dr. Sloan points out, however, that steps are being taken by the American Cancer Society and the American Society of Gastroenterologists in response to this problem: both societies are active in establishing training programs and materials; and the American Society of Gastroenterologists is also attempting to develop an examination for certification in colonoscopy. The influence of the American Cancer Society in the development of colonoscopy is not a recent event. As Dr. Pollard points out, the ACS, through Warren Cole and its Colon Cancer Committee, was the first "organization" to express interest in colonoscopy. (117)

It is apparent that the modern era of fiberoptic endoscopy has now gained a foothold and its widespread application is just beginning. Although progress has been relatively rapid, there have been several factors which slowed application. Perhaps the major stumbling blocks were the problems and time required for instrument development, difficulties brought on by the anatomy and the contents of the colon itself. (118) Another slowing factor was the general lack of enthusiasm, or even interest, on the part of medicine. From the standpoint of aesthetics, the large bowel is not appealing to work with. Developmental efforts were in progress at only a few (two or three) medical institutions in the United States. According to Dr. Pollard, many did not accept the idea that it was possible to introduce an instrument into the colon. What would he do to speed things up if he had the opportunity again? "Be more aggressive in pushing it." (119)

#### Early Detection: Proctosigmoidoscopy

Fiberoptics has provided a new diagnostic capability in the colonoscope. It has not had the same effect in changing the nature of sigmoidoscopy.



Although flexible instruments are becoming available, sigmoidoscopy is still essentially unchanged and based on rigid 25-cm instrumentation that has been used for decades. Many practitioners still prefer the open tube 25-cm rigid sigmoidoscope because of the ease with which biopsy can be accomplished. (120) This is not to say that sigmoidoscopy, as it is used today, is ineffective. As noted earlier, approximately 60 percent of all colorectal cancers occur within the range of this instrument, when used in the hands of an experienced endoscopist. Unfortunately, in the hands of an inexperienced user, frequently it is only the distal 15 to 18 cm of the bowel that are examined. (121)

Further development and utilization of a flexible fiberoptic sigmoidoscope may result in a significant improvement by extending the range of examination to the entire rectosigmoid, up to the junction with the descending colon. (122) The importance of this is underscored by Dr. Overholt:

Perhaps the manufacturers will then return to the point of origin of much of the initial investigative work in this field--the development of a flexible fibersigmoidoscope for routine use, as most of the significant pathology is within reach of an effective 60-cm flexible fibersigmoidoscope. (123)

Indeed, the initial efforts in fiberoptic endoscopy of the federal Cancer Control Program were oriented toward stimulating the development of a flexible proctosigmoidoscope. (124) The hope was that a flexible scope would be more acceptable than the rigid instruments and thus allow expansion of the routine use of proctosigmoidoscopy as a screening procedure for rectal cancer. This hope was never fully realized.

Under the influence of the gastroenterologists, the development of the fiberoptic device went in the direction of a diagnostic instrument for



the entire colon (an instrument six feet long). The federal Cancer Control Program's original intent for a screening instrument was lost because of the professional preoccupation with diagnosis and treatment, rather than routine screening. Dr. Lewis Robbins, the chief of the federal Cancer Control Program at the time, expressed his disappointment in a recent interview.

We wanted a 25 to maybe 50-cm instrument that any family doctor could use....[But] it went in the direction that would give the greatest aid to the profession, the gastroenterologist and the surgeon.

Most colon-rectal cancers you can do something about are in that first foot. You cannot justify putting a fiberoptic instrument into everybody's cecum, periodically, but you could justify the first foot periodically, even in the hands of a family doctor. (125)

The momentum of the new fiberoptic technology carried the development into areas that were evidently judged to be more challenging. As a result, the opportunity still exists for the further development of a flexible instrument with a range of 50-60 cm that would be appropriate to use for case-finding in the hands of a family doctor or trained technician. Is such an instrument needed? Does proctosigmoidoscopy have a role in screening?

The majority of physicians do not routinely include proctosigmoidoscopy for case-finding in the physical examination of asymptomatic patients. (126) Evidently, most consider proctosigmoidoscopy, the endoscopic examination of the distal most part of the large bowel, to be too costly and time-consuming to be applied indiscriminately as a screening or case-finding procedure. It is generally reserved for the investigation of a patient who has been identified as high risk through the presence of such factors as associated medical conditions, symptoms,

or positive results on a screening test. As shown in Table 4, age itself provides a useful indicator of risk for cancer of the colon and rectum. Inspection of the age distribution of the 34,769 cases diagnosed in the Third National Cancer Survey provides insight into the relationship between age and colorectal cancer: 93.3 percent of the victims were age 50 and above, while 71.1 percent of all cases occurred in persons 65 or over. (127)

Table 4: Age-Specific Incidence Rates for Cancer  
of the Colon and Rectum Combined

<u>Age</u>	<u>Cases/100,000</u>
< 9	---
10-14	0.1
15-19	0.3
20-24	0.9
25-29	1.9
30-34	3.5
35-39	7.3
40-44	14.8
45-49	31.6
50-54	51.9
55-59	88.5
60-64	130.3
65-69	197.8
70-74	265.4
75-79	357.0
80-85	414.5
85 +	386.2

Source: Cutler, S. J. and Young, S. L. (128)

The American Cancer Society considers age alone enough of a risk factor so that it recommends annual proctosigmoidoscopic examination of all individuals 40 years of age and older. Since almost eighty million people fall into this age category, if ACS policy were to prevail, 15,000 people working full time would be required to endoscopically examine this population annually. Some investigators suggest that the age be increased to 50 to allow greater concentration on the group that will most likely benefit from the examination, and that the frequency of proctosigmoidoscopy be decreased to every two years in those asymptomatic individuals with no other risk factors. (129) This would reduce the screening load to one-third of the ACS requirements. However, the low yield of cancer even in this group creates problems in screening.

The problem of low yield in the general asymptomatic population is illustrated by Dr. William J. Garrett, a surgeon at the Royal Hospital for Women in Sydney, Australia.

[I]f one man armed with a sigmoidoscope examines one patient every 20 minutes from 9 am to 5 pm Monday to Friday, with an hour off for lunch, and to make it easier restricts his practice to patients aged 50 years and over, he will find one carcinoma of the rectum every 26 weeks. (130)

In the United States the incidence of rectal cancer in the general population age 50 and over is about 52 or 53 cases per 100,000, and on this basis, Garrett's calculations applied to the U.S. would result in the detection of one rectal cancer every 18 weeks. Rectal cancers (including cancer of the rectosigmoid junction) comprise about one-third of all cancers of the large bowel, but this goes up to 60 percent when rectal cancers are grouped with those of the sigmoid colon. (131)

To the extent that cancers as far up the large bowel as the sigmoid colon can also be detected by proctosigmoidoscopy, the above figures on yield should be increased by about three-fourths to be more reflective of the potential of proctosigmoidoscopy (i.e., about one cancer would be detected every 10 weeks).

It is the impressive figure that 60 percent of a very common cancer is within the range of proctosigmoidoscopy that undoubtedly prompts some physicians to advocate routine screening in the asymptomatic population. However, a careful look at the practicality of this position in terms of yield, cost, and acceptability has not been undertaken in a comprehensive and explicit fashion. This is due in part to the fact that an analysis of this nature is complicated by at least several factors, one very important factor being the lack of understanding of the natural history of large bowel cancer, illustrated by the continuing controversy as to whether certain neoplastic but benign appearing polypoid lesions, called adenomatous polyps, eventually contribute or lead to malignancy. The yield of proctosigmoidoscopy is completely different depending on whether one includes more than just cancer itself in the tally.

It should be noted that the important role of proctosigmoidoscopy for case-finding in the symptomatic patient is seldom challenged. Furthermore, the morbidity associated with the procedure is not of sufficient magnitude to unduly hinder its use. The only hazard of any real significance associated with the technical aspects of its use is perforation of the bowel. Fortunately, this serious problem is rare and is reported to occur in only .002 percent to .07 percent of examinations. (132)



Historically, the factors limiting the application of proctosigmoidoscopy in screening have not included morbidity but rather cost and time requirements, along with less than complete acceptability by the screenee, the latter being a factor that all too often is not given sufficient consideration. Because proctoscopy is being advocated as a mass screening tool in some quarters, a question arises whether the feasibility of its application in mass screening should not be investigated further. Of course another important question, one that should be posed for any screening procedure, is whether screening by proctosigmoidoscopy has an impact on colorectal cancer mortality. Consideration needs to be given to the testing of this question in a controlled prospective study.

The fact remains that proctosigmoidoscopy is basically a tool suited for case-finding and diagnostic investigation in symptomatic individuals and in individuals with some other basis for suspecting a disorder. In an analogous situation, few would propose that colposcopy, a method with similar characteristics of application, serve as the basis for a mass screening of asymptomatic women. In fact, the factors which limit proctosigmoidoscopy as a screening tool in the asymptomatic are also claimed to have resulted in its underutilization even among those presenting with symptoms. This view is expressed by Dr. Robert J. Bolt, a professor of internal medicine at the University of California.

Failure to perform proctosigmoidoscopy in the presence of minor symptoms is undoubtedly the greatest repetitive error occurring in day-to-day practice. The necessity for emphasizing its use in these situations must be repeated over and over again. Reasons for failure to heed these warnings are apparent. Although valid excuses, they include the inescapable facts that, 1. preparation for this examination is not welcomed by

the patient as a pleasant procedure, 2. the procedure itself, despite some feeble claims to the contrary, is neither pleasant nor completely free of morbidity and mortality, and 3. this is indeed a "time-consuming procedure" and for most physicians time is at a premium. (133)

The utilization of newer flexible instruments with the incorporation of fiberoptics will potentially decrease patient discomfort, lower morbidity even further and very likely improve physician acceptance. However, these improvements will likely be in gradual increments, ultimately resulting in instrumentation that extends the range of examination by bridging the current diagnostic gap between colonoscopy and rigid 25 cm proctosigmoidoscopy through further development of a 50-60 cm flexible sigmoidoscope.

### Summary

. Control of the most common form of cancer in the United States has not been advanced to any great extent during the past quarter century. Almost 100,000 new cases of large bowel cancer are diagnosed each year, and about half of these are fatal. Improvement in the control of this disease is likely to be dependent upon the potential contribution of screening and diagnostic procedures. The slow pace of progress in the screening and diagnosis of colorectal cancers is in contrast to the experience with cervical cancer, where the past quarter century involved taking an early advance, demonstrating reproducibility, and then moving it into general application as a means of accelerating a pre-existing downward trend in mortality.

. Two procedures in particular, that have become only recently available, contain potential to add to previous capability and bring about

improvement in control: the stool guaiac test and colonoscopy. For colonoscopy, the most notable advance came in 1958 with technological developments in fiberoptics and their incorporation into endoscopy. Before this time there was little attention given to improving and extending direct visualization as a means of colorectal cancer detection and diagnosis. Once research and technological development in flexible fiberoptic endoscopy began it was revolutionary, ushering in a new era in endoscopic capability, with important implications for the more effective control of colorectal cancer.

. The development of colonoscopy was slow in contrast to upper GI fiberoptic endoscopy because of the anatomical nature and contents of the large bowel. The primary factor slowing the subsequent utilization of colonoscopy was, and still is today, the training and experience necessary for its successful use. It is not a procedure for the non-specialist.

. Fiberoptic endoscopy, and colonoscopy in particular, is a major contribution to diagnosis; however, its role in screening is obviously limited for practical reasons. Fortunately the stool guaiac test holds promise in this area.

. The development of chemical tests for detecting fecal occult blood has been evolutionary, with no single event being particularly pivotal. It has taken until the late 1960s and early 1970s for a test of this nature to be shown of practical value in cancer detection. Initial experimentation started over a half century ago and was focused on identifying a chemical test procedure with sensitivity to blood in the stool. Further study was needed to establish a reasonable balance be-



tween false negative and false positive reactions. Subsequent development and study was unproductive until the importance of diet was established and recognition was given to the method of sample acquisition as a means to improve results. Only today has a chemical test for fecal occult blood, primarily the stool guaiac test, been developed and preliminarily tested to the point where it represents a useful means of screening.

. The current status of the control of colorectal cancer was recently reviewed in a monograph authored by Drs. J. P. Welch, G. A. Donaldson and C. E. Welch of the Massachusetts General Hospital in Boston.

The problem of cancer of the colon is far from solved.... Two ways that seemed promising a decade ago have been exploited almost to the limit. At that time there was hope that cure rates could be improved by shortening the interval between onset of symptoms and surgical treatment or by lowering operative mortality. (134)

They reviewed possible tactics of control that are available today and commented:

If the most profitable of these tactics were chosen from the point of view of increasing the number of cures, those most likely to be helpful would be a vigorous attack on polypoid lesions (involving the use of proctosigmoidoscopy and colonoscopy), wide use of the guaiac test as a screening agent [to detect cancer, because, as they point out, the test does not indicate the presence of polyps], wide screening programs for individuals at high risk [for example, those at risk because of hereditary factors], and the identification of patients in whom a combination of surgical procedures and radiation therapy is indicated. Another 10 years will demonstrate whether or not these predictions are correct....(135)

. If the impact is to become manifest in the shortest possible period of time, it appears likely that a national organization or society must take the lead in aggressively advancing the application of available



control measures. The American Cancer Society is involved in furthering application and has an active Colon Cancer Committee but there is need for an organization, such as the National Cancer Institute, to systematically plan and support a definitive assessment and demonstration of the efficacy of available screening and diagnostic approaches, particularly in terms of showing a reduction in colorectal cancer mortality. Until such time as prevention is a more realistic approach to control--made possible if, for example, a breakthrough occurred in controlling dietary carcinogens--the emphasis must be on making rapid and productive use of the means available to detect and cure carcinoma of the colon and rectum.

Chronology of Significant Events in the Development of Test for  
Occult Blood and Fiberoptic Endoscopy

- 1895 Introduction of lighted rigid instrumentation for endoscopic examination of the rectum and the beginning of the era of proctosigmoidoscopy.
- 1900 Experimentation with various chemicals and test procedures to  
to detect presence of occult blood in stool. Effect of factors  
1950 such as diet noted. Little emphasis on development of test procedures suitable for routine screening.
- 1928 First practical demonstration of image transmission through flexible glass fibers.
- 1930s Further development of endoscopy with emphasis on semi-  
to flexible instruments by incorporation of lens systems and  
1950s application to upper GI area--semi-flexible lens gastroscope, miniature intragastric camera.
- 1954 First construction of fiberscope by Hopkins and Kapany.
- 1954  
to Research on improving fiberoptic light transmission.  
1958
- Late Development of sigmoid camera.  
1950s
- 1958 Evidence suggesting that adenomatous polyps may not be forerunners in the development of cancer.
- 1958 Development of first fiberoptic endoscope for gastric diagnosis by Hirschowitz.
- 1958  
to Incorporation of fiberoptics into the rigid sigmoidoscope as a  
1960 means for light transmission.
- 1960s Development of flexible fiberoptic endoscopic instrumentation for examination of large bowel (image transmission).
- 1960s Attention to potential role of chemical test for fecal occult blood in detection of asymptomatic large bowel cancer.
- 1967 First report of successful use of flexible fiberoptic sigmoidoscope by Overholt.
- 1967 Favorable report by Greegor on use of chemical test for detecting asymptomatic large bowel cancer.

Late  
1960s, Development of lower GI endoscopic instrumentation turns toward  
early development of colonoscope.  
1970s

Early Recognition of importance of following specific protocol  
1970s (including special diet) in utilizing chemical test and  
of problem of follow-up on positive tests.

- (1) Silverberg, E., Holleb, A.I.: Major trends in cancer: 25 year survey. CA 25:2-21, 1975.
- (2) Cutler, S.J., Devesa, S.S.: Trends in cancer incidence and mortality in the USA. In Doll, R., and Vodopija, J. (eds.): Host Environment Interactions in the Etiology of Cancer in Man. Lyon, International Agency for Research on Cancer, 1973.
- (3) Axtell, L.M., Chiazze, L.: Changing relative frequency of cancers of the colon and rectum in the United States. Cancer 19:750-754, 1966.
- (4) Cutler, S.J., Myers, M.H., Green, S.B.: Trends in survival rates of patients with cancer. New Eng. J. Med. 293:122-124, 1975.
- (5) See note (4) at 122.
- (6) Levin, D.L., Devesa, S.S., Godwin, Jr., J.D., et al: Cancer Rates and Risks (2nd ed.). DHEW Pub. No. (NIH) 75-691. Washington, D.C.: U.S. Gov't. Printing Office, 1974, p. 91.
- (7) NCI unpublished data.
- (8) See note (6) at 90.
- (9) Burkitt, D.: Epidemiology of cancer of the colon and rectum. Cancer 28:3-13, 1971, at 3.
- (10) Burkitt, D.: Epidemiology of cancer of the colon and rectum. Cancer 28:3-13, 1971.
- (11) Wynder, E.L., Reddy, B.S.: Metabolic epidemiology of colorectal cancer. Cancer 34:801-806, 1974.
- (12) Hill, M.J.: Bacteria and the etiology of colonic cancer. Cancer 34:815-818, 1974.
- (13) See note (6) at 68.
- (14) Turell, R.: Examination. In Turell, R. (ed.): Diseases of the Colon and Anorectum. Philadelphia, W. B. Saunders Company, 1969, pp. 180-216.
- (15) Winawer, S.J., Sherlock, P., Schottenfeld, D., et al: Screening for colon cancer. Gastroenterology 70:783-789, 1976.
- (16) Leffall, Jr., L.D.: Early diagnosis of colorectal cancer. CA 24:152-159, 1974.



- (17) See note (15).
- (18) See note (16).
- (19) Cameron, A.B., Thabet, R.J.: Sigmoidoscopy as part of routine cancer clinic examinations with correlated fecal chemistry and colon cytologic studies. Surgery 48:344-350, 1960, at 349.
- (20) Bell, J.R.: Occult blood in the feces. Guy's Hosp. Rep. 73:20-30, 1923, at 20.
- (21) Bell, J.R.: Occult blood in the feces. Guy's Hosp. Rep. 73:20-30, 1923.
- (22) See note (21) at 20.
- (23) See note (21) at 20.
- (24) Ogilvie, A.G.: Testing for occult blood in feces. Brit. Med. J. 1:755-756, 1927.
- (25) See note (24) at 755.
- (26) Hoerr, S.D., Bliss, W.R., Kauffman, J.: Clinical evaluation of various tests for occult blood in the feces. J.A.M.A. 141:1213-1217, 1949, at 1213.
- (27) See note (26) at 1213.
- (28) Hoerr, S.D., Bliss, W.R., Kauffman, J.: Clinical evaluation of various tests for occult blood in the feces. J.A.M.A. 141:1213-1217, 1949.
- (29) See note (28) at 1217.
- (30) See note (21).
- (31) Leiboff, S.L.: Detection of blood by means of bensidine dihydrochloride. J. Lab. Clin. Med. 14:1186-1191, 1929.
- (32) Morgan, T.E., Roantree, R.J.: Evaluation of tests for occult blood in the feces. J.A.M.A. 164:1664-1667, 1957, at 1666.
- (33) See note (32) at 1666.
- (34) Cameron, A.B., Thabet, R.J.: Sigmoidoscopy as part of routine cancer clinic examinations with correlated fecal chemistry and colon cytologic studies. Surgery 48:344-350, 1960.
- (35) Greigor, D.H.: Diagnosis of large bowel cancer in the asymptomatic patient. J.A.M.A. 201:943-945, 1967.
- (36) See note (35) at 943.

- (37) See note (35).
- (38) See note (15).
- (39) Christensen, F., Anker, N., Mondrup, M.: Blood in feces. A comparison of the sensitivity and reproducibility of fine chemical methods. Clinica Chimica Acta 57:23-27, 1974.
- (40) See note (28).
- (41) See note (15).
- (42) Greigor, D.H.: Occult blood testing for detection of asymptomatic colon cancer. Cancer 28:131-134, 1971, at 132.
- (43) Greigor, D.H.: Occult blood testing for detection of asymptomatic colon cancer. Cancer 28:131-134, 1971.
- (44) See note (15) at 784.
- (45) See note (43).
- (46) Hastings, J.B.: Mass screening for colorectal cancer. Am. J. Surg. 127:228-233, 1974.
- (47) See note (46).
- (48) Telephone interview with Dr. Rulon Rawson, National Large Bowel Cancer Project, M. D. Anderson Hospital and Tumor Institute, by Leon Ellwein of HCCP, January 5, 1977.
- (49) Neuhauser, D., Lewidki, A.M.: What do we gain from the sixth stool guaiac? New Eng. J. Med. 293:226-228, 1975.
- (50) Henning, N., Berry, L.H.: History of gastrointestinal endoscopy. In Berry, L.H. (ed.): Gastrointestinal Pan-Endoscopy. Springfield, Charles C. Thomas, 1974, pp. 5-23, at 6.
- (51) Henning, N., Berry, L.H.: History of gastrointestinal endoscopy. In Berry, L.H. (ed.): Gastrointestinal Pan-Endoscopy. Springfield, Charles C. Thomas, 1974, pp. 5-23.
- (52) See note (14).
- (53) See note (51).
- (54) See note (51) at 11.
- (55) See note (51).
- (56) Salmon, P.R.: Fibre-Optic Endoscopy. London, Pitman Medical Publishing Co., 1974, pp. 1-14.

- (57) See note (51).
- (58) See note (51).
- (59) Tasaka, S., Ashizawa, S.: Studies on gastric diseases using the gastroscope. Bull. Am. Gastros. Soc. 5:12, 1958.
- (60) Matsunaga, F., Tsushima, H., Kubota, T.: Photography of the colon. Gastroent. Endosc. 1:58, 1959.
- (61) See note (51).
- (62) See note (14).
- (63) See note (51) at 18.
- (64) Hirschowitz, B.I., Curtiss, L.E., Peters, C.W., et al: Demonstration of a new gastroscope - the fiberscope. Gastroenterology 35:50, 1958.
- (65) See note (51).
- (66) Colcher, H.: Editorial: Progress in gastrointestinal endoscopic instrumentation in the past decade. Gastrointest. Endosc. 17:4 and 169, 1971.
- (67) Lindgren, N.: Recent device developments. In Ray, C.D. (ed.): Medical Engineering. Chicago, Year Book Medical Publishers, Inc., 1974, pp. 1054-1073.
- (68) See note (56).
- (69) See note (56).
- (70) See note (56) at 4.
- (71) Hopkins, H.H., Kapany, N.S.: A flexible fiberscope, using static scanning. Nature 173:39-41, 1954, at 39.
- (72) See note (56) at 4, 7, and 8.
- (73) Overholt, B.F.: Clinical experience with the fibersigmoidoscope. Gastrointest. Endosc. 15:27, 1968, at 27.
- (74) Telephone interview with Dr. H. M. Pollard, Department of Internal Medicine, University of Michigan, by Leon Ellwein of HCCP, November 11, 1976.
- (75) Turell, R.: Fiberoptic colonoscope and sigmoidoscope. Preliminary Report. Am. J. Surg. 105:133, 1963.
- (76) Overholt, B.F., Pollard, H.M.: Cancer of the colon and rectum. Cancer 20:445-450, 1967.

- (77) See note (14) at 195 and 196.
- (78) See note (75).
- (79) See note (76).
- (80) Overholt, B.F.: Description and experiences with flexible fiberoptic sigmoidoscopes. In Proceedings of the Sixth National Cancer Conference. Philadelphia, Lippincott, 1968, pp. 443-446.
- (81) See note (14) at 201.
- (82) See note (75).
- (83) Wolff, W.I., Shinya, H.: A new approach to the management of colonic polyps. Adv. Surg. 7:45-67, 1973, at 48.
- (84) See note (76).
- (85) See note (80).
- (86) See note (73).
- (87) See note (80).
- (88) See note (76) at 447.
- (89) See note (74).
- (90) See note (74).
- (91) Waye, Jerome D.: The current status of esophagoscopy, gastroscopy, and duodenoscopy. Mt. Sinai J. Med. N.Y. 42:57-80, 1975.
- (92) Winawer, S.J., Sherlock, P., Hajdu, S.I.: The role of upper gastrointestinal endoscopy in patients with cancer. Cancer 37:440-448, 1976.
- (93) Shinya, H., Wolff, W.I.: Flexible colonoscopy. Cancer 37:462-470, 1976, at 470.
- (94) Shinya, H., Wolff, W.I.: Flexible colonoscopy. Cancer 37:462-470, 1976.
- (95) Waye, Jerome D.: Colonoscopy: A clinical view. Mt. Sinai J. Med. N.Y. 42:1-34, 1975.
- (96) Overholt, B.F.: Colonoscopy: A review. Gastroenterology 68:1308-1320, 1975.
- (97) Rasgon, I.M.: Value of proctosigmoidoscopy in colorectal carcinoma. J. Fam. Pract. 2:95-98, 1975.



- (98) Correa, P., Haenszel, W.: Colon and Rectum: Comparative International Incidence and Mortality. In Schottenfeld, D. (ed.): Cancer Epidemiology and Prevention: Current Concepts. Springfield, C. C. Thomas, 1975, pp. 386-403.
- (99) Spratt, J.S., Jr., Ackerman, L.V., Moyer, C.A.: Relationships of polyps of the colon to colonic cancer. Ann. Surg. 148:682-698, 1958.
- (100) See note (99).
- (101) Turell, R., Haller, J.D.: Adenomas of the Colon and Rectum. In Turell, R. (ed.): Diseases of the Colon and Anorectum. Philadelphia, W. B. Saunders Company, 1969, pp. 326-418, at 343.
- (102) See note (15).
- (103) Fenoglio, C.M., Lane, N.: The anatomical precursor of colorectal carcinoma. Cancer 34:819-823, 1974.
- (104) Morson, B.C.: Evolution of cancer of the colon and rectum. Cancer 34:845-849, 1974.
- (105) Horn, Jr., R.C.: Malignant potential of polypoid lesions of the colon and rectum. Cancer 28:146-152, 1971.
- (106) Spratt, Jr., J.S., Watson, F.R.: The rationale of practice for polypoid lesions of the colon. Cancer 28:153-159, 1971.
- (107) Fraumeni, Jr., J.F., Mulvihill, J.J.: Colon and Rectum: Who is at Risk of Colorectal Cancer. In Schottenfeld, D. (ed.): Cancer Epidemiology and Prevention: Current Concepts. Springfield, C. C. Thomas, 1975, pp. 404-415.
- (108) See note (106).
- (109) Gilbertson, V.A.: Proctosigmoidoscopy and polypectomy in reducing the incidence of rectal cancer. Cancer 34 (suppl.):936-939, 1974.
- (110) Wolff, W.I., Shinya, H.: Colonofiberscopic management of colonic polyps. Dis. Colon and Rectum 16:87, 1973.
- (111) See note (101) at 359.
- (112) See note (110).
- (113) Goldhaber, S.A., Bloom, B.S., Sugarbaker, P.H., et al: Effects of the fiberoptic laparoscope and colonoscope on morbidity and cost. Ann. Surg. 179:160-162, 1974.
- (114) See note (96).

- (115) See note (94).
- (116) Interview with Dr. Margaret Sloan, Division of Cancer Control and Rehabilitation, National Cancer Institute, by Devra Breslow of HCCP, November 3, 1975, Bethesda, Md.
- (117) See note (74).
- (118) See note (96).
- (119) See note (74).
- (120) See note (74).
- (121) See note (15).
- (122) See note (15).
- (123) See note (96) at 1317.
- (124) Interview with Dr. Lewis Robbins, by Dr. Lester Breslow and Devra Breslow of HCCP, November 20, 1975, Indianapolis, Ind.
- (125) See note (124).
- (126) Miller, C.J., Reeder, L.G., Manning, H.E.: Every doctor's office - a cancer detection center? CA 14:165-172, 1967.
- (127) Cutler, S.J., Young, J.L.: Third National Cancer Survey: Incidence Data. National Cancer Institute Monograph 41, March 1975, p. 100.
- (128) See note (127) at 102.
- (129) Corman, M.L., Collier, J.A., Veindenheimer, M.C.: Procto-sigmoidoscopy--age criteria for examination in the asymptomatic patient. CA 25:286-290, 1975.
- (130) Garrett, William J.: On the reduction of cancer mortality: Graham Crawford's experiment, 1949-1969. Med. J. Australia 1239-1243, 1970, at 1243.
- (131) DeJong, U.W., Day, N.E., Muir, C.S., et al: The distribution of cancer within the large bowel. Int. J. Cancer 10:463-477, 1972.
- (132) Bolt, R.J.: Sigmoidoscopy in detection and diagnosis in the asymptomatic individual. Cancer 28:121-122, 1971.
- (133) See note (132) at 122.

- (134) Welch, J.P., Donaldson, G.A., Welch, C.E.: Carcinoma of the colon and rectum. Current Problems in Cancer 1:3-61, 1976, at 57.
- (135) See note (134) at 59.





## CHAPTER 7

### CANCER TREATMENT

#### Introduction: Early History

Cancer is almost always a fatal disease if left untreated. This has been recognized throughout the centuries and, as a result, numerous attempts at treatment have been made--always with less than complete success. The approach to treatment has followed closely the concept of disease that was held during the various periods of history. The use of the word, cancer, and the crab as a pictorial symbol for the tumorous abnormality, is attributed to a celebrated second century physician named Galen. He is reported to have noted: "In the breast we often find a tumor in size and shape closely resembling the animal known as the crab, for as in the latter the limbs protrude from either side, so in the tumor the swollen veins radiate from its edges and give a perfect picture of the crab." (1)

During this early period Galen's views came to establish the basis for the study and treatment of cancer (and all other disease). His views are characterized as representing a humoral theory of disease, that all disease could be attributed to an excess or deficiency of one of four basic body fluids: black bile, blood, yellow bile, and phlegm. Galen attributed cancer to an excess of black bile and therapy took the form of various dietary regimens, purgation, ointments, caustic pastes, and sur-

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gical excision. It was not until the seventeenth century that the humoral theory of cancer gave way to the view that cancer began as a local lesion and spread by way of the lymphatics to regional nodes and, finally, to distal sites through the blood. In the nineteenth century, with the development of the microscope, the significance of a single transformed cell was stressed as the first event in the genesis of cancer. This multi-step view of cancer's progression--cell/tissue/lymphatics/blood--provided the foundation for attempts at complete eradication by cutting out the disease while it was still in a localized stage. Radical surgery was advocated when it was judged that the disease might have spread beyond its immediate site of origin to the surrounding regional lymphatic nodes. With developments in control of hemorrhage, anesthetics for relief of pain, and asepsis, surgery moved into the forefront of cancer treatment. (2)

However, just as surgery made great strides against cancer during its evolution throughout the nineteenth century, so too significant progress was made against specific types of cancer by the advent of X-irradiation and modern-day chemotherapy during the twentieth century. As X-ray became available in the early 1900s, its capacity to destroy cancerous cells caused it to be considered immediately as a potential treatment method. At various points in time during the advancement of radiotherapy, it has indeed been shown to be effective against an increasing number of tumors.

For patients whose disease had spread to various parts of the body or for those cancers which involve the hematologic system from the outset, surgery and irradiation seldom provided the means for control. For these

diseases, the last quarter century has seen a revival of medicine in the form of drugs that can be administered systemically--drugs that have been found to be destructive of cancerous cells to a greater extent than normal cells. Drug therapy, or chemotherapy, has historically been used alone for palliative treatment and in combination with surgery or irradiation as curative treatment. Even more recently, it has been used in combination with immunotherapy to enhance the patient's inherent immune mechanisms.

To illustrate the contemporary achievements that have been made in the control of cancer through treatment, certain cancers against which major progress has been made will be reviewed here as case studies. The following sections of this chapter highlight historical events in the development and utilization of surgery, X-irradiation, and chemical modalities in cancer control.

The position of surgery as the cornerstone of cancer treatment is presented by way of its early contribution to treatment of breast cancer, followed by an identification of various unsuccessful challenges to its preeminent status in breast cancer treatment. The two other major treatment modalities, radiation therapy and chemotherapy, are introduced and then discussed in greater detail by consideration of the control of Hodgkin's disease and acute lymphocytic leukemia, two diseases for which surgery has not been effective. Some of the early contributions of multimodality treatment are illustrated through a review of its successful application to Wilm's tumor. The recent emphasis on aggressive multimodality, prolonged treatment is reflected in a return to breast cancer and a review of recent developments which suggest that even for this cancer,



surgery is being recognized as only one component in a composite treatment regimen. A brief overview reflects on the pace of progress during the past quarter century.

### Surgery: Breast Cancer

Breast cancer, a disease that is easily accessible to direct inspection and the surgeon's knife, has been influenced to a great extent by developments in surgical technique. Based on knowledge concerning lymphatic spread, Dr. William S. Halsted introduced the radical mastectomy for the treatment of breast cancer in the 1890s at the Johns Hopkins University. (3,4) His procedure involved removal of the breast itself, including all axillary nodes and pectoral muscles. The procedure significantly changed the outlook for survival of breast cancer patients and soon became the accepted treatment for essentially all cases. (5)

There was no serious challenge to surgery as the treatment of choice for breast cancer (and most other solid tumors) until the post-World War II period. By this time X-ray had been in use for almost half a century, and, with improvements in technology and knowledge about its effect on various tumors, X-irradiation as a means of treatment was beginning to reach a position of respectability and use at various institutions. Assessment of end results using surgery, irradiation, and various combinations of these two modalities was beginning to receive attention, and some physicians were claiming improvement in survival with the addition of postoperative radiation therapy. (6) In fact, treatment of breast cancer by surgery alone was being questioned.



A major challenge to treatment by surgery alone came in 1950 when McWhirter, a radiotherapist at the Royal Infirmary of Edinburgh, published data showing that improved results were obtained with a multi-modality regimen that began with a less radical surgical procedure, called a simple mastectomy, followed by irradiation of the regional nodes. (7) Probably because of the soundness of his data and the attractiveness of less radical surgery, his procedure was enthusiastically accepted by many. However, it has been noted that this enthusiasm was later moderated after further study pointed up problems with local recurrence of the disease and "long term results did not measure up to that of radical mastectomy." (8) Accordingly, surgery continued as the mainstay of breast cancer treatment.

The 1950s saw the state of breast cancer therapy clouded by variations in the surgical procedure itself. In an attempt to improve on the survival results obtained with the classic radical mastectomy, some surgeons were performing even more extended surgery which involved dissection within the mediastinum and neck. The ultra-radical nature of this procedure is evident from a comment made in a review of breast cancer surgery, written in 1953, which characterized this extended radical mastectomy as bordering on "humanectomy." (9)

With the advent of megavoltage radiation therapy in the late 1950s, the potential contribution of irradiation was opened to further investigation, particularly since previous data based on low-beam energy were clearly dated. The disagreement among "authorities" on how breast cancer should be treated continued unabated and, by 1958, the National Cancer Advisory Council of the National Cancer Institute entered the picture with a resolution to initiate and fund a randomized clinical trial to test the

efficacy of radical mastectomy versus simple mastectomy with post-operative irradiation. (10) This study was never undertaken, however, apparently because of continuing professional doubts about the relative efficacy of simple mastectomy. Ultimately, a multi-institution controlled study of radical mastectomy followed by postoperative radiation was started in late 1961. The upshot of all this was that the lack of consensus on appropriate treatment for breast cancer grew rather than lessened.

To further complicate matters, during the 1960s it was suggested on the basis of preliminary data that simple mastectomy without irradiation might be as effective as radical mastectomy in patients without palpably involved axillary nodes. (11,12) A concern for the disfiguration and deformity associated with traditional breast surgery, and its attendant physical and psychological impact on the patient, has recently led a few surgeons to go further yet and advocate a breast-preserving partial mastectomy for certain patients with small localized lesions. (13) Others are calling this a "great step backward" and claim that patients are being "advised to seek, and even to demand, inadequate treatment." (14) In response to the controversy about the surgical treatment of operable breast cancer, the American Cancer Society issued a policy statement in 1973 which, based upon a review of published literature, recommended against limited surgical procedures that remove less than the entire breast. (15)

Breast cancer, which represents the most common cancer in women, has received and will continue to receive a great deal of attention since there still is no unanimity of opinion regarding optimal treatment. It is

apparent that a significant amount of investigation has already taken place within numerous institutions, but this previous work has not been very effective in providing the basis for reaching a consensus in treatment strategies. (As will be noted in a subsequent section, the role of chemotherapy is a factor in this lack of unanimity.) A major weakness of all studies prior to the late 1950s was their retrospective nature, with obvious differences in the composition of the various study populations. Reported favorable results could always be discounted as pertaining to specially selected, unrepresentative groups of patients. Today, the randomized clinical trial is the only generally accepted method of investigation. But this is a recent development; and it has only been in the last decade or so that we have seen the results of a few breast cancer treatment regimens that have been investigated in prospective, randomized clinical trials.

Has the history of investigative effort resulted in a significant improvement in cure rates? Evaluators must look to the impact of surgery, since surgery has been clearly the mainstay of treatment in this century. Except for the most recent decade, the emphasis has been on achieving local and regional control of the disease. While there has been some improvement in length of survival over the past half century, this can be attributed to earlier case finding, with a resulting increase in patients with localized disease at the time of primary treatment. In addition, improvements in surgical support have no doubt contributed to improved survival rates. In many instances we are increasing patient survival time without curing the patient; death from breast cancer still takes place. In fact, the death rate has remained fairly constant. (This is at least a

modest achievement by itself, as some would point out, in the face of an increasing incidence.)

Within the past decade investigations have continued in the hope of improving local or regional control, but recognition that breast cancer has many characteristics of a systemic disease has focused particular attention on curative treatment regimens that go beyond surgery and radiotherapy. An increasing emphasis has been put on chemical treatment as an adjuvant to surgery, and preliminary short-term results hold promise.

The present day incorporation of systemic chemotherapy in the treatment of what is characterized as local disease is evidence that the concept of cancer as a multi-step progression from a single neoplastic cell is no longer considered dictum, even for solid tumors. Cancer is being viewed as a disease of an entire tissue with an early possibility of occult micrometastasis.

#### Radiation Therapy: Hodgkin's Disease

Shortly before the end of the nineteenth century, in 1895, the discovery of X-rays was announced by Wilhelm Conrad Röntgen. (16) Cancer was an early target of this new advance. Twenty-three days after the announcement, X-rays were used in an attempt to treat breast cancer by a manufacturer of Crookes tubes, which was part of the apparatus used to produce X-rays. Because the equipment needed for producing X-rays was available in any well equipped physics laboratory, there was an immediate flurry of enthusiastic activity seeking to use X-rays for therapeutic purposes in hospitals and physicians' offices. Almost simultaneously, the



injurious effects of X-rays were being recognized, and investigation of their biological effects was initiated. Technological improvements in equipment were soon to follow which, in turn, allowed measurement and greater control over the radiation dosage in both diagnostic and therapeutic applications. (17)

During the first half of the twentieth century, malignant growth in all its varieties was attacked with X-rays. Both superficial and deep-seated disease was addressed. Cancers that were difficult to manage with the surgeon's knife were given particular attention. (Hodgkin's disease was such a cancer.) Much was learned about radiation therapy during this period, including the fundamental recognition that X-rays have the power to inhibit cellular growth and even completely destroy cells. The base of knowledge about X-irradiation continued to grow through clinical observation and biological studies, and soon it was recognized that different types of cells and tissue vary in their sensitivity to radiation. Increasingly, the complexities involved in treating cancer by X-irradiation were being recognized. In a 1945 review of the first fifty years of radiation therapy, G. E. Pfahler of the University of Pennsylvania remarked about the developing technique.

Knowledge and skill in the use of this instrumentality are as important as knowledge and skill in the use of the instruments in surgery and more difficult of attainment because the immediate effects cannot be seen. (18)

Today, we realize that there are effects of irradiation that take decades before they become evident and that this manifestation of delayed effects includes cancer itself.

The development of radiation therapy as an effective weapon in the control of cancer is illustrated through a review of its application to

Hodgkin's disease. A comprehensive review tracing historical and contemporary advances in Hodgkin's disease has been recently completed by a modern day pioneer in its treatment, Henry S. Kaplan. (19) His review includes the discussion of several key historical events:

- . Lymph node disease was first described by Thomas Hodgkin in 1832.
- . The name "Hodgkin's disease" was proposed by Sir Samuel Wilks in 1865.
- . William A. Pusey, in 1901, was apparently the first to treat Hodgkin's disease with X-rays. (20)
- . Modern radiotherapy for Hodgkin's disease began in the 1920s with the work of Rene Gilbert, who began to report durable responses to treatment. (21) He was the first to irradiate fields beyond those known to be diseased.
- . Although early data by Gilbert demonstrated a doubling of survival, he, along with other authors of that era, reported data from retrospective studies in an inconsistent fashion, often with unfavorable cases omitted from the results; this reporting on only selected cases contributed to the subsequent neglect of his pioneering concepts of treatment.
- . The first reasonably convincing evidence that X-ray therapy extends the survival of patients with Hodgkin's disease was presented by C. B. Craft in 1940 from data collected on patients treated between 1926 and 1939. (22) He reported five-year survival of 23.4 percent as compared to 5.8 percent in an untreated group of patients from 1910 to 1939.

- . Craft's paper did not attract widespread attention and the curative potential of radiotherapy was not recognized until 1950 when Vera Peters published a now classic paper reporting a five-year survival of 51 percent and 10-year survival of 25 percent in a series of 113 patients treated from 1924 to 1942. (23) She reported 88 percent five-year survival in those patients with early disease, and pointed out the importance of high doses in achieving cure.
- . By the 1960s, a sufficient period of time had elapsed so that it was now possible to observe that no significant decrease in survival took place between the tenth and twentieth year, and thus there was finally evidence to support the view that Hodgkin's disease was indeed curable by irradiation.

A technological milestone in the development of radiation therapy was the advent in the 1950s of X-ray machines with megavoltage energy levels. One of the leading figures in the megavoltage era of radiotherapy (and undoubtedly the leading figure in Hodgkin's disease) was Henry Kaplan. Dr. Kaplan intensively investigated the treatment of Hodgkin's disease, and in 1962 published highly encouraging initial results obtained through the use of high-beam energy and high tumor dosage. (24) Boosted by these initial results, Dr. Kaplan extended megavoltage therapy with curative intent to cases with widespread disease. As the role of irradiation in the treatment of Hodgkin's disease steadily progressed, three parameters emerged as being of central importance to the achievement of cure: an extended field of irradiation; high dosage; and high-beam energy. (25)

Effective application of these potentially hazardous concepts has not been possible without a simultaneously increasing sophistication in the measurement of the extent of disease. Progressive refinements in the classification of patients to enable an optimal tailoring of the treatment to probable disease extent have been a clear part of successive improvement in radiation therapy results. The first widely accepted clinical staging classification was proposed by Vera Peters in 1950 as part of her pioneering work. (26) Subsequent refinements were proposed by Peters and Middlemiss to take account of both anatomic extent of detectable disease and signs and symptoms. (27) This was then modified and expanded to a four-stage system by Kaplan in his early work with megavoltage therapy. (28) General adoption of a four-stage clinical staging system was reached in 1965 at an International Symposium on Hodgkin's disease in Rye, New York. (29) As experience increased, further changes were proposed, and at a 1971 conference held in Ann Arbor the current system was officially recommended for use. (30) Table 1 reproduces this clinical staging classification. (See next page).

Do other treatment modalities have any role in the therapeutic control of Hodgkin's disease? During the time that irradiation was making inroads, the potential role of surgery in Hodgkin's disease was also being investigated, at least to a limited extent. However, little of lasting value in the surgical cure of Hodgkin's disease has resulted. The use of surgery over the past decades is summarized by Kaplan.

During the period from about 1920 to 1950, there was also some interest in the use of radical surgery for the eradication of localized lymphomas. However, in most of the series in which good results were reported, X-ray therapy had been given postoperatively and, therefore, could well have been responsible for the favorable outcome. This consideration and the cosmetically disfiguring end results



Table 1: Clinical Staging Classification in Hodgkin's Disease

Stage	Definition
I*	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I <sub>e</sub> )
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II <sub>e</sub> )
III	Involvement of lymph node regions on both sides of the diaphragm (III) which may also be accompanied by involvement of the spleen (III <sub>s</sub> ) or by localized involvement of an extralymphatic organ or site (III <sub>e</sub> ) or both (III <sub>se</sub> )
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

\*The presence or absence of fever, night sweats, and/or unexplained loss of 10% or more of body weight in the six months preceding admission are denoted by adding the suffix letters B and A, respectively.

Source: Kaplan and Rosenberg (31)

of such extensive surgery have gradually led most surgeons to consider that radical surgery is not indicated in the primary management of the malignant lymphomas. (32)

The development of the role of chemotherapy in Hodgkin's disease has been more promising from the outset. The initial clinical tests of the effectiveness of chemicals in combating cancer were in cases of Hodgkin's disease and other malignant lymphomas. (33) Since the first trial during World War II, the developments in chemotherapy have had a significant impact upon Hodgkin's disease patients. Single agents were tried first for palliation of advanced disease and then, prompted by the early results of combination chemotherapy in acute lymphatic leukemia, trials of combination chemotherapy for advanced Hodgkin's disease were introduced in 1963. (34) The results from this pilot study at the National Cancer Institute, utilizing a four-drug regimen, led to a significantly expanded study of another four-drug combination, MOPP (vin-cristine, nitrogen mustard, procarbazine, and prednisone), in 1964. This combination has now been shown to be highly effective. Using MOPP, researchers at the NCI were able to obtain complete remissions in 80 percent of their patients with advanced Hodgkin's disease; and of these patients, 70 percent have remained alive for five years or longer, and 40 percent have been free of disease without maintenance therapy. (35) As a result of this and other investigations, the usual therapy of choice for advanced Hodgkin's patients is treatment with six or more courses of MOPP. (36,37) Although high rates of remission and lengthened duration have been demonstrated, leading to speculation about cure, it should be recognized that continued follow-up and evaluation is necessary to determine whether Hodgkin's disease can, in fact, be cured by drugs.

The success with advanced (and recurrent) disease has stimulated further trials to evaluate the use of similar chemotherapy combination with irradiation in the management of earlier stages of Hodgkin's disease. (38) Although there have been reports of previous attempts to use chemotherapy as an adjunct to irradiation in early disease, the results were not remarkable, probably because of the agents used and deficiencies in patient staging and management as measured by current standards. (39) However, with the improved rates of induction of complete remission, followed by prolonged duration even in face of the burden presented by advanced disease, the prospect for improving cure in early disease by using combination therapy continues to be an active area of investigation.

Table 2 lists the current recommended therapeutic approaches for previously untreated patients with various stages of Hodgkin's disease. Estimates of five-year relapse free survival that can be expected are also given along with treatment regimens that are currently being tested to further improve the estimated results. Data on five-year survival (not necessarily disease free) from a more recent source indicate that with aggressive therapy from 80 to 90 percent of patients in stages I, II and III and almost 40 percent of those in stage IV achieve this milestone. (40) The ten-year disease free survival in this same group of 504 patients was about 50 percent, which reflects the permanent cure rate that can now be achieved in Hodgkin's disease.

Experimental therapy aside, the curative treatment of Hodgkin's disease is, today, clearly based on radiation therapy. Over the past two decades, with developments in megavoltage equipment and therapeutic tech-

Table 2: Treatment of Hodgkin's Disease

Stage of disease	Recommended therapy	Estimated 5-year disease free survival (%)	Experimental therapy
IA, I <sub>e</sub> A IIA, II <sub>e</sub> A	Total lymphoid radiotherapy	90	Limited radiotherapy + Combination chemotherapy
IB, I <sub>e</sub> B IIB, II <sub>e</sub> B	Total lymphoid radiotherapy	75	Total lymphoid radiotherapy + Combination chemotherapy
IIIA, III <sub>e</sub> A III <sub>s</sub> A II <sub>s</sub> A, II <sub>s</sub> B	Total lymphoid radiotherapy	60	Combination chemotherapy + Total lymphoid radiotherapy
IIIB, III <sub>e</sub> B III <sub>s</sub> B	Total lymphoid radiotherapy or Combination chemotherapy	40	Total lymphoid radiotherapy + Combination chemotherapy
IVA, IVB	Combination chemotherapy or Palliative approaches	25 0	Total lymphoid radiotherapy + Combination chemotherapy Sequential chemotherapy

Source: Rosenberg, S.A. (41)



nique, treatment with curative intent has been appropriate in an increasing percentage of patients. Initially only the 10 to 15 percent of patients in stage I were treated curatively; but today essentially all but stage IV patients can be treated curatively with radiation therapy. As already noted, recent progress in combination chemotherapy has been such that this modality is now considered as a partner in the management of patients with advanced (stage IV) disease. Of course, when the individual case does not offer a reasonable prospect for cure, chemotherapy continues to be the major treatment for palliation.

Reflecting on the progress that has been achieved with this disease, Dr. Kaplan states:

The dramatic improvement in the prognosis of Hodgkin's disease which has been recorded during the past decade may be attributed primarily to three factors: 1. more thorough diagnostic evaluation of the extent of disease in each patient, aided particularly by lymphoangiography and staging laparotomy; 2. modern techniques of intensive megavoltage radiotherapy employing large fields shaped to encompass multiple lymph node chains in continuity; and 3. combination chemotherapy, employing a battery of drugs which share activity against Hodgkin's disease but have non-overlapping toxicities. (42)

In this way a disease that affects both the young and the old is slowly being conquered. The disease has an annual prevalence in the United States of about three cases per hundred thousand population, with almost half of the victims dying. (43) Fortunately, significant progress has already been made, trends in survival rates are dramatically upward, (44) and mortality rates are dropping. (45) The outlook for control of the disease can be characterized as optimistic.

## Acute Lymphocytic Leukemia

The logical starting point for the initial clinical study of chemotherapy was in patients with systemic disease. Little beyond establishing the diagnosis and treatment of the clinical manifestations (fever, infection, hemorrhage, pain) was available to alter the poor prognosis associated with cancers that were systemic in nature. Acute lymphocytic leukemia was just such a disease. It is the most common malignant disease in children, with a general incidence of three to four per 100,000 preschool children; however, the disease occurs in all age groups, and the rate in the general population is one per 100,000. (46) Before the advent of modern chemotherapy, death would occur in most cases within weeks or a few months after the onset of symptoms. After a diagnosis of acute leukemia, there was little that could be done for the patient. Today, with optimal treatment, the potential exists to extend the median survival to five years with the objective of treatment now being cure. (47)

As already noted, efforts directed toward the utilization of drugs to cure cancer are traceable to the early periods of recorded history. During the subsequent centuries, numerous chemical agents were put forth as having curative effects on malignant disease. It was not until the 1940s that the modern era of chemotherapy had its beginning, that is, the use of a systemically administered drug to extend the survival of patients with cancer. C. B. Huggins of the University of Chicago, who developed the rationale behind the use of hormone therapy in patients with disseminated cancer of the prostate, (48) is credited with ushering in this new era. Huggins and his co-workers developed the concept of the

hormonal dependence of prostatic epithelium through studies undertaken in dogs. Based on investigations relating prostatic atrophy to changes in hormone status, Huggins initiated the use of a relatively simple surgical procedure (orchiectomy rather than open prostatectomy) in conjunction with estrogen therapy as the preferred treatment for prostatic cancer. The revolutionary nature of this work is evident when one considers the thinking that prevailed at the time. Reflecting on the work of Huggins and his associates, Alfred Gilman of the Albert Einstein College of Medicine (who became involved in the early development of chemotherapy) observed:

In the minds of most physicians the administration of drugs, other than an analgesic, in the treatment of malignant disease was the act of a charlatan. (49)

As noted by Joseph H. Burchenal of Memorial Sloan-Kettering Hospital in presenting the Fifth Annual David A. Karnofsky Memorial Lecture:

Even after these discoveries [chemotherapy of infectious disease], however, as late as 1945, Woglom (50) described the search for antitumor agents as follows: "Those who have not been trained in chemistry or medicine, which after all is only applied chemistry, may not realize how difficult the problem of treatment really is. It is almost--not quite, but almost--as hard as finding some agent that will dissolve away the left ear, say, yet leave the right ear unharmed: so slight is the difference between the cancer cell and its normal ancestor." (51)

Dr. Huggins shared the Nobel Prize for Medicine and Physiology in 1966, in recognition of his initiation of the drug (hormonal) treatment of cancer.

Another early milestone, the investigation of the role of toxic chemicals in combating cancer, was a byproduct of military investigations of chemical warfare agents. The first unclassified publication reviewing



basic investigations of their biological action was in 1946 for the nitrogen and sulfur mustards. (52) Reference is made to "cautious preliminary trials" to test the possible effectiveness in the treatment of neoplasms. The first clinical trial actually took place in December, 1942 (while the work was classified) when an "X-ray resistant patient in the terminal stages of lymphosarcoma" was treated with nitrogen mustard. (53,54) As pointed out in a review by Dr. Gilman of this initial clinical trial, nitrogen mustard was classified top secret at the time, and the entry in the patient's chart simply referred to "compound X given intravenously." (55) Nitrogen mustard is related chemically to another alkylating agent, sulfur mustard, which is a war gas known since the late 1800s, and, as Dr. Gilman observed, "perhaps no compound had been more thoroughly studied prior to clinical trial than were the nitrogen mustards." In fact, the potential of these agents in the treatment of cancer could have been recognized earlier. As noted by Joseph H. Burchenal:

...There was...a very careful study...in 1919 on autopsy material from soldiers dying of exposure to mustard gas in World War I, which demonstrated the damage to bone marrow and lymphoid tissue caused by this agent. This...remained almost unnoticed for many years, because it was an idea before its time and investigators failed to grasp its possible practical significance. (56)

Thus it was not until a quarter century later, with the advent of another world war and a renewed interest in war gases, that further observation and the introduction of alkylating agents in the systemic treatment of the lymphomas were undertaken.

Chemotherapy took a major step forward with the work of Sidney Farber and his colleagues. In 1948 Sidney Farber, a pathologist, and his colleagues at the Children's Medical Center in Boston reported the first



evidence of improvement with 10 out of 16 seriously ill acute leukemia patients. (57) This favorable response was obtained by administering a powerful and toxic drug, aminopterin (a folic acid antagonist) by intramuscular injection. What led to the selection of this agent? Prior to this event, folic acid conjugates had been tested for possible antineoplastic activity in patients with acute leukemia, but postmortem studies showed that just the opposite was happening: the course of disease was actually accelerated. As noted by Farber,

[I]t appeared worthwhile, therefore, to ascertain if this acceleration phenomenon could be employed to advantage...by the administration of antagonists to folic acid. (58)

The first folic acid antagonists were weak and had little or no clinical effect. However, laboratory and postmortem study provided sufficient encouragement so that when the more potent antagonist, aminopterin, became available it was tried and found to be effective. In a recent review of the role of folate antagonists in cancer chemotherapy, the contribution of Farber and his co-investigators was characterized in this way.

This demonstration was a landmark in antineoplastic chemotherapy: it provided the first demonstration that an antimetabolite could be an effective antineoplastic agent, and provided the stimulus for the development of other antimetabolites as possible antitumor agents. (59)

Beginning with enthusiasm generated by these initial results, there was continued progress in extending the survival of patients. In a step by step fashion, one drug after the other was synthesized and tested for antileukemic effect. Aminopterin was closely followed by a more effective and related compound, methotrexate, which was then successively followed

by other active agents which became available, including prednisone in 1950, 6-mercaptopurine (6-MP) in 1952, cyclophosphamide in 1957, and vincristine in 1960. (60) These effective drugs were matched both sequentially and in combinations to determine whether the total effect would be greater than that achieved by use as single agents. It was also recognized that by continuing to administer drugs during remission, the duration of remission could be extended. By using prednisone or vincristine, remission rates of 50 to 60 percent were being attained, and this was increased beyond 80 percent when both were used in combination; by combining this further with the use of 6-MP, methotrexate, and cyclophosphamide for remission maintenance, a median remission duration of six months could be achieved. (61) By the 1960s, the advantages of chemotherapy regimens involving combinations of drugs were established. Another important milestone was reached.

The introduction of combination therapy was possible because of several important developments. Particularly important were: quantitative laboratory investigations of tumor cell proliferation; identification of different ways to interfere in the mechanism of action; the presence of single agents that were already identified as being active through study in clinical trials; and pharmacologic studies which showed that many of these active drugs had different and non-overlapping toxicity. Building on this experience and knowledge, the first major program of combination chemotherapy was introduced by Freireich and his co-workers (who were at the National Cancer Institute at the time) and applied to the treatment of acute lymphocytic leukemia of children. (62) This program of intensive intermittent combination therapy using four drugs

(VAMP: vincristine, prednisone, 6-MP and methotrexate) demonstrated the increase in remission induction and duration that could be achieved with acceptable side effects.

The contribution of chemotherapy in extending the survival of children with acute lymphocytic leukemia was clearly evident, and this all had been achieved in little more than a decade. Yet investigators recognized that death from the disease was only being postponed. A careful analysis of the improvement in survival showed that it was almost entirely due to the time spent in remission. Essentially all patients eventually relapsed, even though a second or third remission could commonly be induced. Cure had not been achieved but, nevertheless, the progress that had been made gave great hope for further improvement in acute leukemia and other cancers. As a result, the attitude of the profession toward some of the incurable cancers was changing. A new era of cancer treatment had arrived. This optimism was noted by Dr. Farber upon receiving the Albert Lasker Clinical Research Award in 1966.

The most important therapeutic weapons forged in the last 20 years are the anticancer chemicals, hormones, and the antibiotics. Their discovery and application marked the beginning of the era of chemotherapy of cancer, which may be described after 20 years as disappointing because progress has not been more rapid, and optimistically because of demonstrated accomplishment against a small number of cancers in man.

We now know that a form of cancer [acute leukemia], widely disseminated throughout the body, apparently can be destroyed and caused to disappear for months or years with the restoration of the patient to a state of health indistinguishable from the normal by the action of any one of at least five chemicals or combinations of these. Even though this does not represent cure, this achievement gives justifiable hope that chemicals alone may one day destroy completely this and other forms of cancer. (63)



The enthusiasm and momentum created by the success of early chemotherapeutic investigations had an influence on the organization of clinical cancer research in several ways. Because of the increased interest in investigative explorations involving drug synthesis, screening, pharmacology, and methodology, a number of drug development and clinical chemotherapy programs had been established at several institutions by the 1950s (the Sloan-Kettering Institute for Cancer Research, the Children's Cancer Research Foundation, the Columbia University College of Physicians and Surgeons, the Lankenau Hospital-National Cancer Institute Collaborative Program, and Stanford University School of Medicine). Soon there were more clinicians ready to test drugs than there were new drugs available. Capacity for preclinical screening of new agents was limited and it was recognized that the drug development evaluation task was too complex to be pursued effectively by individual institutions without some degree of coordination. After a considerable amount of discussion and evaluation by professional and public groups, the National Cancer Institute organized in 1955 a broadly based cooperative national chemotherapy program, the Cancer Chemotherapy National Service Center. Under the direction of C. Gordon Zubrod of the National Cancer Institute, this program greatly expanded the discovery, testing, and application of new cancer drugs. (64)

Another result of the interest in chemotherapeutic investigations was a narrowing of the communications gap between the basic science community and the clinician. In moving beyond the trial and error of testing one drug after another, great emphasis was placed on utilizing data from experimental studies to facilitate the design of potentially optimum com-



bination regimens for clinical trial. This required developing an understanding of mechanisms of action, time-dose relationships, and other considerations of biochemical pharmacology. The laboratory scientist worked side by side with the clinician in programs concerned with developing effective antileukemic agents. A truly interdisciplinary approach was being taken.

During this period, the utility of targeted research efforts such as that conducted in cooperative group studies was underscored. For example, the systematic study of chemotherapeutic control of acute lymphocytic leukemia was facilitated through a cooperative group established in 1956. This international group of physicians and scientists, titled the Acute Leukemia Group B, accelerated the exploration of chemotherapy through numerous protocol studies. Relying upon this well-organized approach, many institutions were able to participate in research studies that otherwise would not have been feasible because of the relatively small number of patients at any individual institution. This helped to extend the reach of clinical research into a larger number of institutions, all focused toward a common set of objectives and research hypotheses.

What has this period of discovery, evaluation, and organization produced? Today, it is possible to achieve remission in 90 percent of patients with acute lymphocytic leukemia. As a means of prolonging remission duration, several antileukemic agents are now being administered prophylactically for three and even four years. The recurrence of the disease frequently manifests itself in the central nervous system as meningeal leukemia. The central nervous system is a sanctuary for tumor cells because of the inability of current chemotherapeutic agents to

effectively cross the blood-brain barrier. Therefore, to eradicate clinically undetectable leukemic cells, the central nervous system is also treated. The present day therapeutic approach of proven effectiveness for acute lymphocytic leukemia involves the use of prednisone and vincristine for remission induction, and intrathecal methotrexate, generally in combination with cranial irradiation, for the treatment of the central nervous system. (Building on previous work at the Memorial Sloan-Kettering Hospital and the Children's Medical Center in Boston, Pinkel (65) and his co-workers at St. Jude Hospital in Memphis have been credited with pioneering this present day method of central nervous system prophylaxis. (66) ) In some instances, craniospinal radiation without chemotherapy is used for central nervous system treatment. This is followed by weekly methotrexate and daily 6-MP for maintaining remission, and periodic administration of vincristine and prednisone for reinforcement. (67,68)

The prevention of relapses continues to be the thrust of clinical research. By extending the relapse free period, survival is lengthened until ultimately the disease might be considered cured. Although only four years of data are available, the best regimen currently under study in the 26 centers that are members of Acute Leukemia Group B is supportive of a statement that with aggressive total treatment strategies it should now be possible to achieve five-year survival in 50 percent of acute lymphocytic leukemia cases. (69) It is important to realize, however, that to achieve results that reflect the optimum treatment available, the patient through his physician must have access to increasingly complex but effective treatment protocols.

How far are we from actually achieving this target? Survival data from a diverse group of 33 hospitals, somewhat representative of experience of the general population of children and adolescents with acute lymphocytic leukemia diagnosed from 1965-1969, indicate that the median survival time was 16.8 months. (70) Comparison with national end results evaluation data for acute lymphocytic leukemia diagnosed during 1955-1964 with a median survival time of 9.5 months reveals an increase of 77 percent, reflecting the improvement associated with the modern day usage of combination chemotherapy. Comparison of data from institutions participating in the Southwest Cancer Chemotherapy Study Group protocols during the time period 1958-1970 shows a further increase of 20 percent to about 20 months median survival time. Even more recent data for patients entered on Acute Leukemia Group B and the Children's Cancer Study Group protocols show a median survival of nearly three years. (71,72) Unfortunately, the complexity of current treatment regimens raises questions regarding the feasibility of control through general community physicians. Optimal patient management frequently requires the expertise of a specialist in medical oncology.

Recognizing that today something must be done to close the gap between treatment results achieved within the general medical community and those achieved in specialized centers, the Division of Cancer Control of the National Cancer Institute has become active in carrying new treatment regimens into the community. It is attempting to do this by supporting the development of networks of community physicians in cooperation with cancer centers to provide the best treatment available at any point in time to the general population. As described by Dr. Myron Karon of the University of Southern California:



Physicians are identified with the requisite experience, oncological expertise, and facilities for supportive care to carry out such a treatment program in the community in cooperation with the center. Techniques are set up to monitor the results and compare them with matched patients treated in various research centers and co-operative groups. When better therapy is identified in research centers, the new treatment approach can be rapidly disseminated throughout the network. When no potentially curative treatment is available, or when one can identify prognostic categories that may require intensive therapy beyond the capabilities of the community, then such patients should be referred and treated at the center, with follow-up care in the community. (73)

Although the improvement that has been achieved in survival of patients with acute lymphocytic leukemia has been spectacular, it is still considerably short of cure, and research must be pursued as vigorously in the future as it has been in the past. As noted by Dr. James F. Holland, a national figure in medical oncology:

Access to patients [by cooperative groups and research centers] is a major factor that influenced the pace of arriving at curative chemotherapy sooner. A delicate balance exists between the private practice of medicine in making available today's achievements, and the conduct of ongoing clinical research to attain the ultimate objective. (74)

Much remains to be done, including some aspects of research that have received relatively little attention. Dr. Karon points out a perplexing problem.

Up to now, the cooperative group approach has been to increase the intensity of treatment delivered to all patients in an effort to prolong the median survival. Since such intensive therapy might interfere with host defense, this approach could shorten the survival of some patients while improving the survival of others, producing a net effect which might not be measurable. (75)

It is clear that increased attention needs to be given to the host-treatment interactions, both over the short and long term. Although there may be reluctance to stop long term therapy that has been successful



in maintaining remission, it is in these long term survivals that the cumulative effects of therapy are unknown and may pose a significant risk to the patient. In fact, unexpected side effects are being identified. (76) Just as the initial efforts in drug testing moved closer to the basic sciences, and particularly biochemical pharmacology, to obtain requisite knowledge of drug-dose relationships in extending the therapeutic effectiveness of agents in eradicating tumor, today there is increasing reliance upon fundamental knowledge in such areas as immunology and radiobiology to understand the complexities and effects of therapy on the host in general. Furthermore, as therapy becomes increasingly effective, proper evaluation requires a corresponding greater commitment of time and effort, a factor which in itself slows the rate of advancement.

#### Wilms' Tumor

Wilms' tumor (nephroblastoma) is a malignant disease of the kidney that occurs almost exclusively in young children. The first case of a probable renal tumor in an infant was reported in 1814 by T. F. Rance. (77) The name Wilms' tumor resulted from classic studies and description of the tumor by a German surgeon named Max Wilms. (78) The tumor may develop in any part of the kidney and remains encapsulated when it is small, but as it grows, it can rupture the kidney capsule. Diagnosis is generally based on the finding of an abdominal mass discovered by the child's parents or by a physician during a routine examination. Because of its rapid and frequently nonsymptomatic growth, it is commonly a sizeable mass by the time it is detected. Although it is one of the more common cancers in children, like all childhood cancers it has a low incidence. The current incidence is almost five cases per 100,000 children under five years of age. (79)

Advances in treatment within the past four decades have gradually changed this once fatal disease to one in which cure is being achieved in a significant majority of cases. Today, Wilms' tumor is treated with a combination of three modalities: surgery, irradiation, and chemotherapy. Accordingly, it represents, perhaps, one of the best examples of successful treatment that utilizes multiple modalities. What has been the historical background of this achievement?

As with solid tumors in general, surgery in one form or another was the only recourse available after a diagnosis of Wilms' tumor. Since surgery did not result in any significant cures, irradiation was attempted by several clinical investigators. Postoperative irradiation was introduced in 1915, (80) irradiation was used alone in 1916, (81) and preoperatively in 1923. (82) Preoperative irradiation was used as a means of shrinking the tumor and lowering operative mortality and as an attempt to prevent dissemination of the tumor (some disagreed and felt that it increased the spread of tumor). In these early investigations, the number of cases treated was small and the reporting of results did not present a convincing argument that any significant improvement could be obtained by one method over the other. However, interest increased and an important advance took place during the 1930s when William Ladd, a surgeon at the Children's Hospital in Boston, recognized two factors that appeared important in increasing survival in patients treated surgically: the tumor could be spread by palpation or biopsy; the tumor grows rapidly and surgical removal should take place immediately after diagnosis. (83) Ladd was not in favor of preoperative irradiation, but noted that postoperative irradiation might be shown to be effective after further evaluation. He

did not believe in preoperative irradiation because of his conviction that tumors of essentially any size could be removed by the transperitoneal approach and, therefore, preoperative irradiation was not justified with its risk of permitting tumors to metastasize during the long period of irradiation.

Gross and Neuhauser, also at Children's Hospital, reviewed all cases of tumors of the kidney treated up to 1947 at their institution and reported the following statistics. (84) In 27 cases treated from 1914 to 1930, the probable cure rate (which they defined as survival greater than one-and-a-half years) was 14.9 percent; this reflected varying treatment methods used by a number of visiting surgeons. From 1931 to 1939, 31 cases were treated with a probable cure of 32.2 percent, reflecting the improvements in surgical technique introduced by Ladd. From 1940-1947, 38 cases were treated with essentially the same surgical procedures as the preceding period but with the addition of postoperative radiation in all but two cases. The rise in cure rate to 47.3 percent was attributed largely to the routine postoperative irradiation of the renal bed. Ladd had initially suggested that because mortality was generally rapid in treatment failure, cure was probably achieved if the disease did not recur or metastasize within a year-and-a-half. (85) More recent evidence is generally supportive of this early measure of cure. (86)

That there was still not agreement on a common effective treatment regimen by this time was pointed out in a review and evaluation of treatment methods by R. M. Harvey in 1950. (87) He noted that there were advocates for five different treatment plans--irradiation alone, surgery alone, preoperative irradiation, postoperative irradiation, and both pre-operative and postoperative irradiation--and after an extensive review



of the literature for all reported cures of Wilms' tumor, the most commonly used and effective method was the last one. The combination modality therapy of surgery and irradiation appeared to have been firmly established by this time, with two-year survival rates of up to 40 percent.

The next significant advance in improving the prognosis of Wilms' tumor came about with the incorporation of chemotherapy in the treatment battery. As with other childhood tumors, Sidney Farber and his co-investigators at the Children's Cancer Research Foundation and Hospital in Boston were leading the way. Because over half of Wilms' tumor patients were still dying of the disease, Farber and his colleagues at Children's Hospital began in 1946 to incorporate various anticancer chemicals, such as methotrexate, in the management of children with Wilms' tumor. This was done with a twofold purpose: prevention of metastasis and treatment of metastasis. Success was not immediate. A subsequent review of survival data from 1946 to 1954 showed little change in survival rates from the preceding ten-year period. (88)

Based on information concerning toxicity and anticancer action in experimental animals, actinomycin D was used in the treatment of Wilms' tumor in the mid-1950s and was found to be the first active agent. Subsequent studies at the Children's Hospital and by investigators elsewhere supported the effectiveness of the administration of actinomycin D at the time of surgery followed by radiation therapy. In patients without evidence of metastasis at the time of diagnosis, the two-year survival rate (essentially equivalent to cure) was increased to almost 90 percent and in those patients with metastasis treated curatively the survival rate approached 60 percent; this was a group in which prior cure was virtually hopeless. The data based on patients seen from 1957-1964 clearly present



the contribution of chemotherapy in multimodality treatment. The importance of employing curative combination chemotherapy from the beginning is underscored in that only a 39 percent two-year survival was achieved in a separate group of patients without metastasis at diagnosis whose treatment was begun elsewhere before being referred to the Children's Hospital. (89)

As part of the general thrust in chemotherapy during the 1960s, studies were undertaken to find agents of increasing effectiveness. Vincristine was introduced in the early 1960s and was found to be comparable in effectiveness to actinomycin D in Wilms' tumor, and more effective in other childhood cancers. (90)

By the 1960s, three different cooperative groups (Acute Leukemia Group B, Children's Cancer Study Group A and Southwest Cancer Chemotherapy Study Group) were carrying on concerted efforts in the study of combination therapy for Wilms' tumor and other childhood cancers. Because of the relative rarity of the disease, it was soon recognized that it was not feasible for any of these cooperative groups to individually mount a prospective randomized clinical trial and expect definitive answers to the numerous questions about the effectiveness of various therapeutic regimens in a reasonable period of time. As a result, these three cooperative groups, along with various other specialty groups, joined forces in a collaborative effort to increase the number of patients who would be entered onto common protocols. The study group that resulted in 1968 was called the National Wilms' Tumor Study Group. (91,92)

The formation of this collaboration was of great importance, and remains so today, if answers to clinical research questions are to be obtained in a timely fashion. Even with a pooling of patients from the participants in the National Wilms' Tumor Study Group, the accrual rate is slow since there are only about 800 new childhood cases of Wilms' tumor discovered annually throughout the entire United States. (93) The immediate objectives of the Group were: to determine whether postoperative radiation is necessary in patients with completely resectable tumor confined to the kidney; and to determine which of the two active agents (actinomycin D and vincristine) is more effective and whether it is possible to achieve a net effect that is greater than that obtained separately with either drug when both are administered concurrently. (94)

Today, Wilms' tumor is a disease that is coming under control. Immediate surgery to excise the tumor mass and careful staging, radiotherapy to render nonviable all cancer cells that may have escaped into the tumor bed during excision, and adjuvant chemotherapy on a prolonged intermittent basis to prevent the development of metastases have provided the foundation for cure in a majority of patients. This planned integration of surgery, irradiation and chemotherapy has changed a devastating disease into one that is curable in over 80 percent of patients with localized disease and about 50 percent in those with metastatic disease. (95)

### Breast Cancer Revisited

The present potential of surgery in the cure of breast cancer was, for the most part, apparently reached decades ago. Radiation therapy has been effective in reducing local recurrences, but without evidence of any

major increase in survival. The systemic nature of the disease is being increasingly recognized. Physicians, after treating a patient by the previous methods of radical surgery, radiation, or short-term single agent chemotherapy, frequently regarded five-year survival as suggestive of cure. But, in fact, the likelihood of dying from breast cancer is no different in the 15th year than in the third year after diagnosis; the rate of dying is approximately eight percent per year in the group at risk. (96) Only after two decades does survival approach normal life expectancy. (97) With this and other evidence, it is now thought that micrometastases are already present at the time of surgery, particularly in patients with positive nodes.

The success of aggressive multiple drug chemotherapy in such cancers as leukemia and advanced Hodgkin's disease has led to the use of chemotherapy as a prophylactic adjuvant to surgery in breast cancer, as well as in other solid tumors. The new approach to treatment is to use surgery, followed possibly by radiation therapy for local and regional control, and adjuvant chemotherapy to prevent metastases. It is hoped that the cure rate which has been essentially constant for 40 years can now be significantly improved through the contribution of prolonged adjuvant chemotherapy. (98)

The first agent used as an adjuvant to surgery in a large-scale clinical trial was Thio-TEPA, a drug that had been shown effective in palliation of breast cancer. The purpose of the investigation, undertaken in 1958 by the newly formed National Surgical Adjuvant Breast Project (NSABP), was to determine if the drug was effective in eliminating cells that might be dislodged into the blood or lymph system as a result



of surgical manipulation. By 1964-1965, it was apparent that the results of the study would be disappointing. Although in a subgroup of patients who were premenopausal, with four or more positive nodes, there had been a short-term improvement in recurrence and survival rates, over the longer term there was no significant improvement in any category of patients. A second phase of the same study evaluated 5-Fluorouracil (5-FU) and found that it could not be recommended as an adjuvant to breast surgery because of its severe toxicity and apparent lack of therapeutic effect. (99,100)

The effect of this initial trial was to discourage for years the further systematic study of adjuvant chemotherapy. At least one small-scale feasibility study using methotrexate in a subgroup of patients was initiated in 1968, but it was soon abandoned after high toxicity was noted early in the study. The deterrent to further research that had been created by past failure was described by Bernard Fisher, the Chairman of the NSABP, in 1972. (The NSABP had stopped all chemotherapy studies and was concentrating its efforts on a clinical trial of the relative merits of surgery with and without irradiation.)

[I]t was impossible for this country's most eminent medical oncologists to reach an agreement as to what drug(s) should be employed, let alone what regimen with a particular drug would be acceptable. The number of different opinions was equivalent to the number of individuals whose advice was sought! Partly because of the lack of unanimity, and partly because of the fear that since the first adjuvant study had not resulted in a positive contribution and "we could ill-afford another failure," little interest could be mounted to carry out such a study.

Unless compromises of conviction on the part of a substantial number of investigators can be attained, future trials will not succeed and more delay will result. It cannot be too strongly emphasized that



the medical community must be prepared to accept the responsibility that every clinical trial will not result in positive findings. Such a happening should not result in a national melancholia, as in the past, which prevents additional trials being carried out. (101)

Dr. Fisher went on to point out that "solo therapeutic adventurism," the use of an agent outside of the context of a clinical trial, is not the answer either and should be discouraged. At the time of Dr. Fisher's remarks, which were made in 1972, a new clinical trial involving prolonged surgical adjuvant chemotherapy with the drug L-Pam was in the final design stages, and some of the institutions in the NSABP, along with certain members of two other cooperative groups, indicated their intent to participate. (102)

The new clinical trial, using L-Pam (L-phenylalanine mustard) as an adjuvant to radical mastectomy in patients with advanced breast cancer, was initiated in 1972 and the NSABP reported early findings in 1975. (103) The agent was being administered for up to two years after surgery. (In the thio-TEPA study the drug was administered only immediately after surgery.) With an average follow-up period of nine months, it was found that L-Pam provided significantly greater protection against recurrence in premenopausal women; although a similar trend was observed in postmenopausal patients, the preliminary findings were not statistically significant.

One of the factors influencing the choice of L-Pam for this large-scale study was an earlier, more limited study, of L-Pam and a three-drug combination called CMF -- cyclophosphamide, methotrexate, and fluorouracil. (104) Both regimens were found to be active, particularly the combination, and so both were suggested for treatment of advanced breast cancer. As already noted, L-Pam was studied further by the NSABP, and

evaluation of CMF was begun by a group from the National Cancer Institute of Italy.

After 27 months of study and a mean follow-up period of 14 months, the Italian group, headed by G. Bonadonna, reported preliminary results which indicate that prolonged cyclic administration of CMF is highly effective as an adjuvant treatment to radical mastectomy in reducing the recurrence rate in breast cancer patients with positive axillary lymph nodes. (105) This statistically significant effect was observed in all subgroups of patients (not just premenopausal). It remains to be seen whether this favorable trend continues, or whether it will be limited to the short-term, having no significant impact on breast cancer mortality.

The immediate effect that these preliminary findings are having on clinical research is illustrated in an addendum to a review paper by Carbone. (106) In the paper he reviews (as of October, 1974) the treatment arms (regimens) of six randomized breast cancer adjuvant studies, each containing a radical mastectomy alone arm. However, in the addendum which was prepared after the paper was accepted for publication, he notes that subsequent changes in the trials identified have resulted in four of the groups dropping the mastectomy alone arm, leaving this arm in only two groups, one of which is the Italian study referenced above.

Although the results have been greeted with general enthusiasm from both the public and physicians, (107) there have been several cautions expressed that the results be considered experimental rather than as proven. (108,109) One concern is that because the health effects of

long-term chemical prophylaxis are unclear, it may be unwise to enter any but those at highest risk into protocol studies.

Indeed, the unknown risk of aggressive and prolonged therapy is a topic which is receiving increasing attention, particularly in those patients for whom significant short-term progress has been made by the use of aggressive therapy. The need exists for long-term follow-up of patients, not just for evaluation of treatment, but also to permit early detection of any possible adverse effects of the treatment. This is particularly true in children, who may need follow-up for life even if considered cured. The importance of being able to optimize treatment in order that cure can be effected with a minimum amount of treatment is a new topic. Dr. D'Angio of the Memorial Hospital for Cancer and Allied Diseases in New York states:

The understandable tendency to add more treatments to existing regimens in attempts to obtain better suppression of both local and remote disease must be viewed in the light of what is becoming known regarding the late effects of treatment....The concept that a little treatment is good, and that a lot more is a lot better clearly does not pertain to the treatment of malignant diseases in children, with all their vagaries, and the potential deleterious consequences of the therapies employed. (110)

#### Reflections on the History of Cancer Treatment

The treatment of cancer has had a long history marked by both successes and failures. Surgery, irradiation, and chemotherapy (including hormonal and endocrine therapy) are all established parts of the contemporary armamentarium. New methods, such as immunotherapy, bid to become included as modalities of proven effectiveness. A new era of



cancer treatment is upon us--the era of aggressive multi-modality therapy with curative intent. The thinking behind the trend to multi-modality therapy has been described by Dr. Joseph Burchenal:

Surgery and radiotherapy are limited not only by the bulk of the tumor, but by its dissemination, whereas...chemotherapy [and immunotherapy] is limited by the mass of the tumor rather than by its dissemination. (111)

[D]espite the fact that even large localized tumors can be cured by surgery, cancer is by its very nature a metastasizing disease and if it has spread beyond the field of surgery, even in microscopic amounts, it is no longer curable by surgery alone. The same problem holds for radiotherapy. With chemotherapy, however, the reverse situation occurs--the drug spreads throughout the body, except perhaps in certain pharmacologic sanctuaries such as the brain, and is able to seek out the cancer cells and destroy them wherever they happen to be. The problem is that chemotherapy is limited by the mass of the tumor rather than its extent....If, on the other hand, you remove the bulk of the tumor with surgery or radiotherapy, and...chemotherapists, either alone or with...immunotherapists, treat the micro-metastasis likely to be already present...we stand a good chance of curing the patient. (112)

What has been the historical process by which new treatment regimens are developed and then adopted by the general medical community?

Unlike attempts at the control of cancer through prevention or screening for disease, the translation of clinical research advances into effective control strategies, followed by their widespread utilization, has taken place almost exclusively within the established physician-centered medical care delivery system. Because the transfer of treatment technology from research to control and service has taken place primarily within a single sector of the health care system, large-scale organized efforts involving a wide spectrum of health professionals were seldom needed to move clinical advances into the hands of the practicing physician.



. Over the years the development of new approaches to cancer treatment has paralleled the conceptualization of the disease. Breast cancer represents a good example where the historical development of treatment methods followed closely the concept of the disease. Without much resistance from any segment of medicine, radical surgery as the primary means of treatment for breast cancer developed its potential fairly early. Results with radical surgery were dramatic; accordingly, acceptance of this procedure as the treatment of choice came rapidly. In subsequent investigations, the role and appropriate extent of surgery has continued to receive attention. But without demonstrable improvement associated with any of the proposed alternatives to radical mastectomy, this traditional treatment modality retains its preeminent position.

. The development of the role of X-irradiation in the treatment of Hodgkin's disease also progressed with a minimum of opposition. When substantial gains in survival could be demonstrated with the use of radiotherapy, the technique created a momentum of its own. Success followed success and the gains were propelled by both advances in equipment technology and the genius of modern-day investigators such as Kaplan.

. Early developments in chemical therapy came similarly. Although most practitioners were skeptical, little opposition was offered to the clinical investigations of such pioneers as Farber, since their work was directed at the dying patient. Because the research was aimed at lethal disease, short term follow-up was sufficient to demonstrate early effectiveness in extending survival. Bolstered by gains against such formidable cancers as leukemia, the development of treatment regimens based

on the utilization of various toxic chemical compounds intensified. This interest came at a time when attention was being placed on large-scale targeted research efforts as a way to speed achievement of a goal. Almost coincidental with the onset of the post-Sputnik space age, researchers and biomedical managers promoted the organization of a large-scale nationwide program as a means to accelerate the development of effective chemotherapeutic agents. The federally funded Cancer Chemotherapy National Service Center was born--a cooperative undertaking involving individual scientists and physicians, universities, research institutes, hospitals, and industry. Congress had expressed its determination to find a means to cure cancer by providing line item budgetary support for this undertaking. The eventual magnitude of the effort in drug development which subsequently evolved led Gordon Zubrod, the program director, to comment:

These [clinical trials] took longer and cost more money than anyone had anticipated except perhaps the pharmaceutical industry. In retrospect, the job was so vast and so complex that only the federal government could have undertaken it. (113)

This enterprise moved therapy by chemical means into the position of a mature treatment modality that is now responsible for producing normal life expectancy in a significant percentage of patients treated for at least 10 types of cancer (found generally in the young).

. Large-scale cooperative investigative efforts, which utilize almost exclusively the prospective, randomized clinical trial, are now the generally accepted method of conducting clinical research. Prospective, randomized studies involving multiple institutions have emerged as the means whereby definitive information on the efficacy of competing treatment

regimens can be arrived at in a relatively short period of time. The earlier pattern of investigators working independently and then reporting their experience on 10 to 20 years of case accumulation has been eclipsed.

. An increasing emphasis is being placed on treatment, aimed against the full spectrum of cancers, with curative rather than palliative intent. The availability of a number of agents, each active against at least one tumor, has created a situation where it is difficult to select agents either individually or in combinations for testing as part of new experimental treatment regimens. Reaching consensus is not merely an academic problem, since the expense and number of patients needed for definitive testing of curative regimens preclude simultaneous initiation of numerous large-scale trials with only small differences between them. Tumors for which traditional therapy provides a significant percentage of cures (such as in breast cancer) are being studied to determine whether mortality has in fact been decreased by the incorporation of a new treatment regimen. This can be a long and expensive undertaking.

. The increasingly complex and sophisticated means of treating cancer have become obstacles in themselves. Simply communicating the existence of a new treatment regimen is not enough. The training and expertise required to implement such treatment regimens may be beyond what can be expected of the general medical community.

. While the momentum created by the discoveries of ever more effective, but also complex, treatment regimens continues, limitations on resources are likely to slow the accelerating development of new multi-modality treatment strategies. Dr. Maxwell Wintrobe, an internist of national acclaim, and an early contributor to the development of chemotherapy, had



these cautionary remarks to offer in both reflecting back upon the advances that have come in chemotherapy and in looking forward to the control of cancer.

I am quite disturbed [by] the enormous sums that are spent on trials of this and trials of that...and the relatively small amount of money that goes to support the pursuit of new ideas. This is a very serious fault and we are heading for doomsday if we don't wake up to this very disproportionate use of funds.

The people who were involved in the development of the National Cancer Act [thought] that if we put enough money into it we could go to the moon....[I]t was only natural for people who know nothing about the history of science and the history of ideas...to think, well, all we need to do to have cancer cured by 1976 is to put money into it and just get a massive program, organize research, organize everybody in the country.... It's understandable how a person who knows nothing about the subject could come to that conclusion. But the fact is that when it came to the moon situation, we had the technology--we had had the technology for 20 or 30 years. It was a matter of organizing technology to do the job we wanted. But in...cancer we don't have the knowledge....What I am worried about is that we are not providing the funds which will encourage people with ideas to pursue their ideas even though they may seem to be farfetched. Who would have thought--we certainly had no idea--we were working on war gas--that that would lead to cancer chemotherapy. We had not the faintest idea. We were doing it because it was a job we were asked to do; we needed to do it; everybody was trying to do everything they could to help in the war effort. And, again, people working on folic acid had no idea that one could develop an agent which was an antifolate which would interfere with the growth of cells....

All of this applied research is [a disincentive to] forcing people who might...be stimulated to sit down and think and to get an idea and pursue that idea even though it has no obvious direct bearing on cancer. There are so many instances in the history of science where the pursuit of an idea without any other objective, except to seek the truth, has ended in information which has been of enormous value.

But then when you stop to think of it, cancer and chemotherapy is after all closing the [barn] door after the horse is gone....We have got to find a way to prevent cancer, and we are doing very little about that. (114)



Chronology of Significant Events in Treatment of Cancer:  
Breast Cancer, Hodgkin's Disease, Acute Leukemia, and Wilms' Tumor

- 1890s    Halsted introduced radical surgery for breast cancer.
- 1895    X-rays discovered by Rontgen.
- 1920s    Kilovoltage energy levels developed in X-irradiation, beginning the modern era of radiotherapy.
- 1939    NCI's radium loan program initiated.
- 1940    First convincing evidence presented demonstrating that the survival of Hodgkin's disease patients is extended by X-ray therapy.
- 1941    Beginning of modern era of chemotherapy by Huggins' demonstration of the therapeutic effect of orchiectomy and hormone therapy in patients with advanced prostatic cancer.
- 1940s    The effectiveness of postoperative irradiation as adjunct to surgical treatment of Wilms' tumor was demonstrated.
- 1946    First open paper presented reporting on the activity of nitrogen mustard against leukemia and lymphoma.
- 1948    Demonstration that folic acid antagonist was capable of inducing short-term remissions in childhood acute leukemia.
- 1950    Initiation of modern day clinical staging classification systems for Hodgkin's disease.
- 1950s    Development of megavoltage energy level radiotherapy.
- Middle 1950s    Randomized controlled trial and cooperative groups initiated as method for conducting clinical research.
- 1955    The Cancer Chemotherapy National Service Center was established.
- 1956    The Acute Leukemia Cooperative Group was established.
- 1958    Formation of National Surgical Adjuvant Breast Project (a cooperative group).
- 1958    Initiation of large-scale clinical trial of chemotherapy (thio-TEPA) as an adjunct to surgery in breast cancer treatment (results were discouraging).
- Late 1950s, Early 1960s    Demonstration of effectiveness of multi-modality treatment (surgery, irradiation, chemotherapy) in the treatment of Wilms' tumor.

- Early Development and testing of treatment regimens utilizing  
1960s combinations of chemotherapeutic agents.
- 1962 First results using megavoltage beam energy and high tumor  
dosage in radiotherapy for Hodgkin's disease patients.
- 1968 Formation of National Wilms' Tumor Study Group.
- 1972 Initiation of second large-scale study of chemotherapy  
(using L-PAM, a combination of drugs) as an adjuvant to  
surgery in treatment of breast cancer.
- 1975 Treatment of 35 hematologic and solid tumor types being  
investigated through 17 cooperative clinical groups.

Notes: Chapter 7

- (1) Harvey, A.M.: Early contributions to the surgery of cancer. William S. Halsted, Hugh H. Young and John G. Clark. Johns Hopkins Med. J. 135:399-417, 1974, at 399.
- (2) Lewison, E.F.: The surgical treatment of breast cancer. An historical and collective review. Surgery 34:904-953, 1953.
- (3) Halsted, W.S.: The results of radical operations for the cure of carcinoma of the breast. Ann. Surg. 46:1-19, 1907.
- (4) Halsted, W.S.: The results of perations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. Ann Surg. 20:497-555, 1894.
- (5) Harvey, A.M.: Early contributions to the surgery of cancer. William S. Halsted, Hugh H. Young and John G. Clark. Johns Hopkins Med. J. 135:399-417, 1974.
- (6) Adair, F.E.: The role of surgery and irradiation in cancer of the breast. J.A.M.A. 121:553-559, 1943.
- (7) McWhirter, B.: Cancer of the breast. Am. J. Roentgenol. 62:335-340, 1949.
- (8) Urban, J.A.: Changing patterns of breast cancer. Cancer 37:111-117, 1976, at 112.
- (9) See note (2) at 931.
- (10) Shimkin, M.B., Koppel, M., Connelly, R.R., et al: Simple and radical mastectomy for breast cancer: A re-analysis of Smith and Meyer's report from Rockford, Illinois. J. Nat. Cancer Inst. 27:1197-1215, 1961.
- (11) Crile, Jr., G.: Results of simplified treatment of breast cancer. Surg., Gynecol. & Obstet. 118:517-523, 1964.
- (12) Crile, Jr., G.: Results of simple mastectomy without irradiation in the treatment of operative stage I cancer of the breast. Ann. Surg. 168:330-336, 1968.
- (13) Crile, Jr., G., Esselstyn, C.B., Hermann, R.E., et al: Partial mastectomy for carcinoma of the breast. Surg., Gynecol. & Obstet. 136:929-933, 1973.
- (14) See note (8) at 112.
- (15) Editorial: American Cancer Society Policy Statement on Surgical Treatment of Breast Cancer. CA 23:341-343, 1973.

- (16) Röntgen, W.C.: Ueber eine neue Art von Strahlen.  
Sitzungsberichte d. physik.-med. Gesellsch. z. Würzburg.  
Dec. 28, 1895, pp. 132-141.
- (17) Pfahler, G.E.: The development of roentgen therapy during  
fifty years. Radiology 45:503-521, 1945.
- (18) See note (17) at 520.
- (19) Kaplan, H.S.: Hodgkin's Disease. Cambridge, Harvard University  
Press, 1972, pp. 1-14 and 279-283.
- (20) Pusey, W.A.: Cases of sarcoma and of Hodgkin's disease treated  
by exposure to X-rays: A preliminary report.  
J.A.M.A. 38:166-169, 1902.
- (21) Gilbert, R.: Radiotherapy in Hodgkin's disease (malignant  
granulomatosis): anatomic and clinical foundations; governing  
principles; results. Am. J. Roentgenol. 41:198-241, 1939.
- (22) Craft, C.B.: Results with roentgen ray therapy in Hodgkin's  
disease. Bull. Staff Meet. Univ. Minn. Hosp. 11:391-409, 1940.
- (23) Peters, M.V.: A study of survivals in Hodgkin's disease  
treated radiologically. Am. J. Roentgenol. 63:299-311, 1950.
- (24) Kaplan, H.S.: The radical radiotherapy of regionally localized  
Hodgkin's disease. Radiology 78:553-561, 1962.
- (25) See note (19).
- (26) See note (23).
- (27) Peters, M.V., Middlemiss, K.C.H.: A study of Hodgkin's disease  
treated by irradiation. Am. J. Roentgenol. 79:114-121, 1958.
- (28) See note (24).
- (29) Rosenberg, S.A.: Report of the Committee on the Staging of  
Hodgkin's Disease. Cancer Res. 26:1310, 1966.
- (30) Kaplan, H.S., Rosenberg, S.A.: The management of Hodgkin's  
disease. Cancer 36:796-803, 1975.
- (31) See note (30) at 797.
- (32) See note (19) at 14.
- (33) Goodman, L.S., Wintrobe, M.M., Dameshek, W., et al: Nitrogen  
mustard therapy. J.A.M.A. 132:126, 1946.
- (34) Devita, Jr., V.T., Canellos, G.P., Moxley, III, J.H.: A decade  
of combination chemotherapy of advanced Hodgkin's disease.  
Cancer 30:1495-1504, 1972.



- (35) See note (34).
- (36) See note (30).
- (37) Goldsmith, M.A., Carter, S.K.: Combination chemotherapy of advanced Hodgkin's disease. Cancer 33:1-8, 1974.
- (38) Rosenberg, S.A., Moore, M.R., Bull, J.M., et al: Combination chemotherapy and radiotherapy for Hodgkin's disease. Cancer 30:1505-1509, 1972.
- (39) See note (38).
- (40) See note (30).
- (41) Rosenberg, S.A.: Hodgkin's Disease. In Holland, J.F., and Frei, III, E. (eds.): Cancer Medicine. Philadelphia, Lea & Febiger, 1973, pp. 1276-1301, at 1295.
- (42) Kaplan, H.S.: The complete clinical oncologist. A new approach to training. Cancer 30:1462-1468, 1972, at 1464.
- (43) Unpublished NCI data.
- (44) Cutler, S.J., Myers, M.H., Green, S.B.: Trends in survival rates of patients with cancer. New Eng. J. Med. 293:122-124, 1975.
- (45) See note (43).
- (46) See note (43).
- (47) Simone, J.V., Aur, R.J.A., Hustu, H.O., et al: Acute lymphocytic leukemia in children. Cancer 36:770-774, 1975.
- (48) Huggins, C.B., Stevens, Jr., R.E., Hodges, C.V.: Studies on Prostatic Cancer II. The effects of castration on advanced carcinoma of the prostate gland. Arch. Surg. 43:209-223, 1941.
- (49) Gilman, A.: The initial trial of nitrogen mustard. Am. J. Surg. 105:574-578, 1963, at 577.
- (50) Woglom, W.H.: General Review of Cancer Therapy. In Moulton, F.R. (ed.): Approaches to Tumor Chemotherapy. Washington, D. C., AAAS, 1947, pp. 1-12.
- (51) Burchenal, J.H.: From wild fowl to stalking horses: Alchemy in chemotherapy. Cancer 35:1121-1131, 1975, at 1123.
- (52) Gilman, A., Phillips, F.S.: The biological actions and therapeutic applications of the B-chloroethyl amines and sulfides. Science 103:409-415, 1946.

- (53) See note (49) at 576.
- (54) See note (33).
- (55) See note (49) at 577.
- (56) See note (51) at 1122.
- (57) Farber, S., Diamond, L.K., Mercer, R.D., et al: Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). New Eng. J. Med. 238:787-793, 1948.
- (58) See note (57) at 787.
- (59) Johns, D.G., Bertino, J.R.: The Chemotherapeutic Agents: Folate Antagonists. In Holland, J.F., and Frei, III, E. (eds.): Cancer Medicine. Philadelphia, Lea & Febiger, 1973, pp. 739-754, at 739.
- (60) Frei, E.: Chemotherapy of acute leukemia. CA 14:252-256, 1964.
- (61) See note (60).
- (62) Freireich, E.J., Karon, M., Frei, III, E.: Combined chemotherapy (VAMP) in the treatment of acute leukemia in children. Proc. Amer. Assoc. Cancer Res. 5:20, 1964.
- (63) Farber, S.: Chemotherapy in the treatment of leukemia and Wilms' tumor. J.A.M.A. 198:826-836, 1966, at 826 and 830.
- (64) Zubrod, C.G., Schepartz, S., Leiter, J.: The chemotherapy program of the National Cancer Institute: history, analysis, and plans. Cancer Chemother. Rep. 50:349-381, 1966.
- (65) George, P., Pinkel, O.: Central nervous system radiation in children with acute lymphocytic leukemia in remission. Proc. Am. Assoc. Cancer Res. 6:22, 1965.
- (66) Burchenal, J.H.: From wild fowl to stalking horses: Alchemy in chemotherapy. Cancer 35:1121-1131, 1975.
- (67) Henderson, E.S.: Acute Lymphoblastic Leukemia. In Holland, J.F., and Frei, III, E. (eds.): Cancer Medicine. Philadelphia, Lea & Febiger, 1973, pp. 1173-1199.
- (68) Simone, J.V.: Management of childhood leukemia. Postgrad. Med. 55:225, 1974.
- (69) Holland, J.F., Glidewell, O.: Oncologists reply - Survival expectancy in acute lymphocytic leukemia. New Eng. J. Med. 287:769-777, 1972.

- (70) Zippin, C., Cutler, S.J., Lum, D.: Time trends in survival in acute lymphocytic leukemia. J. Nat. Cancer Inst. 54:581-586, 1975.
- (71) See note (69).
- (72) Karon, M.: The treatment of acute childhood leukemia: Predictions for the future based on extrapolations from the past. Cancer 35:1000-1006, 1975.
- (73) See note (72) at 1005.
- (74) See note (69) at 777.
- (75) See note (72) at 1004.
- (76) See note (47).
- (77) Rance, T.F.: A case of fungus haematodes in the kidneys. Med. Phys. J. 32:19, 1814.
- (78) Wilms, M.: Die Mischgeschwulste der neire. Leipzig, A. Georgi, 1899.
- (79) See note (43).
- (80) Heimann, A.: Uber Neirentumoren im Kindesalter auf Grund der in Chirurgischen Universitätsklinik zu Freiburg im Bresigau Geobachteten Falle. Freiburg, 1915.
- (81) Friedlander, A.: Sarcoma of the kidney treated by roentgen ray. Amer. J. Dis. Child. 12:328, 1916.
- (82) Reiser, M.P., Creevy, C.D.: Wilms' tumor. Urol. Survey 2:413, 1952.
- (83) Ladd, W.E.: Embryoma of the kidney. Ann. Surg. 108:885-902, 1938.
- (84) Gross, R.E., Neuhauser, E.B.D.: Treatment of mixed tumors of the kidney in childhood. Pediatrics, 6:843-852, 1950.
- (85) See note (83).
- (86) Platt, B.B., Linden, G.: Wilms' tumor: A comparison of two criteria for survival. Cancer 17:1573-1578, 1964.
- (87) Harvey, R.M.: Tilms' tumor: An evaluation of treatment methods. Radiology 54:689-696, 1950.
- (88) Farber, S.: Chemotherapy in the treatment of leukemia and Wilms' tumor. J.A.M.A. 198:826-836, 1966.
- (89) See note (88).
- (90) Wolff, J.A.: Advances in the treatment of Wilms' tumor. Cancer 35:901-904, 1975.

- (91) See note (90).
- (92) D'Angio, G.J.: Management of children with Wilms' tumor. Cancer 30:1528-1533, 1972.
- (93) See note (43).
- (94) See note (92).
- (95) See note (90).
- (96) Mueller, C.B., Jeffries, W.: Cancer of the breast: Its outcome as measured by the rate of dying and causes of death. Ann. Surg. 182:334-341, 1975.
- (97) Brinkley, D., Haybittle, J.L.: The curability of breast cancer. Lancet 2:95-97, 1975.
- (98) Bonadonna, G., Brusamolino, E., Valagussa, P., et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. New Eng. J. Med. 294:405-410, 1976.
- (99) Fisher, B., Ravdin, R.G., Ausman, R.K., et al: Surgical adjuvant chemotherapy in cancer of the breast: Results of a decade of cooperative investigation. Ann. Surg. 168:337-356, 1968.
- (100) Fisher, B.: Surgical adjuvant therapy for breast cancer. Cancer 30:1556-1564, 1972.
- (101) See note (100) at 1560 and 1561.
- (102) See note (100).
- (103) Fisher, B., Carbone, P., Economou, S.G., et al: L-phenylalanine mustard (L-Pam) in the management of primary breast cancer. New Eng. J. Med. 292:117-122, 1975.
- (104) See note (98).
- (105) See note (98).
- (106) Carbone, P.P.: Chemotherapy in the treatment strategy of breast cancer. Cancer 36:633-637, 1975.
- (107) Holland, J.F.: Major advance in breast cancer therapy. New Eng. J. Med. 294:440-441, 1976.
- (108) Costanza, M.E.: The problem of breast cancer prophylaxis. New Eng. J. Med. 293:1095-1098, 1975.
- (109) Krant, M.J.: (letter) Chemotherapy of breast cancer. New Eng. J. Med. 294:549, 1976.



- (110) D'Angio, G.J.: Pediatric cancer in perspective: Cure is not enough. Cancer 35:866-870, 1975, at 869.
- (111) See note (66) at 1127.
- (112) Burchenal, J.H.: Adjuvant therapy--theory, practice and potential. Cancer 37:46-57, 1976, at 47.
- (113) Zubrod, C.G.: The basis of progress in chemotherapy. Cancer 30:1474-1479, 1972, at 1476.
- (114) Interview with Dr. Maxwell Wintrobe, Department of Internal Medicine, University of Utah, by Devra Breslow of HCCP, December 3, 1975, Los Angeles, Ca.



## CHAPTER 8

### THE REHABILITATION AND CONTINUING CARE OF THE CANCER PATIENT

#### I. Introduction

While the public has probably been informed of the fact that there were about 665,000 new cases of cancer diagnosed in 1975 (1), it is probably not generally known that about 222,000 Americans will not die from cancer this year as a result of prompt, definitive treatment. (2) This figure contrasts sharply with the relatively bleak survival rates in the early decades of this century. In the 1930s, fewer than one in five cancer patients survived for five years after being treated. In the 1950s, one in four survived for five years or longer. (3) Now the ratio is more than one in three. (4) In addition, there are about 1.5 million Americans alive today who have been cured of cancer. (5) (While cure is usually defined as survival for at least five years, some patients can be discharged as free of the disease after one year and others after three years, while some may be followed for a period longer than five years.) (6) Since all cancer patients cannot be saved, "continuing care" may be necessary; it is discussed in the last part of this chapter.

In more specific terms, the previous statistics indicate that thousands of people have undergone various procedures such as mastectomies, laryngectomies and other head and neck surgery with possible

alterations in physical appearance, colostomies, and other procedures which require external stomas. What happens to these persons after their treatment has been completed?

Dr. John E. Healey, Jr., Associate Director for Cancer Control at the Comprehensive Cancer Center for the State of Florida in Miami, has observed that rehabilitation is the fourth phase of medicine, after prevention, diagnosis, and definitive treatment. (7)

The term 'rehabilitation' is derived from the Latin and is literally translated 'to make suitable again.' The goal in the rehabilitation of the patient with cancer is to assist him to return to as nearly a normally functioning state as possible. Such efforts must go beyond the physical restoration of the patient and include means to alleviate the social, the psychological, the vocational and economic problems of these patients. (8)

To be sure, the previous definition of rehabilitation is applicable to any person who has recovered not only from cancer but from any disease, whether chronic or acute. Indeed, it has been observed by Dr. J. Herbert Dietz, Jr., Chief of the Rehabilitation Service of the Department of Surgery at Memorial Sloan-Kettering Cancer Center in New York, that "practically the entire classification of possible disabilities is to be found in the cancer patient population." (9) If this is the case, how do the rehabilitation needs of the cancer patient differ from those of any other patient?

The following chapter focuses first on the problems that are unique to cancer patients in general and then continues with an examination of the specific problems of persons who have had cancer of the head and neck, breast, and colon. Finally, this chapter will



assess to what degree the needs of these persons have historically been recognized and met through the efforts of organized rehabilitation programs sponsored by the government and voluntary organizations.

#### In the Isolation Booth: Psycho-social and Economic Considerations

A review of the rehabilitation literature suggests that certain fears are experienced by most, if not all persons who are rehabilitated after an illness. There are fears of being socially unacceptable because of altered physical features or abilities. There is a struggle to accept a changed image of self that may be a result of a modification of appearance or behavior patterns. There is apprehension about regaining a degree of economic or vocational independence comparable to that which the person had attained prior to his illness. But there is one nagging fear that besets the cancer patient in particular--the recurrence of malignancy, especially metastases to another site less responsive to treatment than the original neoplasm. It is an anxiety which must be reckoned with even after the most successful clinical treatment. This is primarily what sets the cancer patient apart from other candidates for rehabilitation. (10)

At the same time that the patient is battling personal apprehension about the recurrence of cancer, he or she must also confront and deal with the social isolation imposed by external forces. In a recent study (11), a psychologist listed 21 disabilities and asked a group of 455 persons--rehabilitation workers, high school, college and graduate students, to rank the disabilities in order of their social acceptability. A ranking at the top of the list indicated that the person interviewed felt little or no "social distance" between himself and a person with that disability. Conversely, a

disability ranked at the bottom of the list was felt by the interviewee to create a greater degree of social distance. The outcome of the study revealed the following ranking (12):

- 1) ulcer
- 2) arthritis
- 3) asthma
- 4) diabetes
- 5) heart disease
- 6) amputee
- 7) blindness
- 8) deafness
- 9) stroke
- 10) cancer
- 11) old age
- 12) paraplegia
- 13) epilepsy
- 14) dwarf
- 15) cerebral palsy
- 16) hunchback
- 17) tuberculosis
- 18) ex-convict
- 19) mental retardation
- 20) alcoholism
- 21) mental illness

As the research indicates, "hidden" physical handicaps such as ulcers, arthritis, asthma, diabetes, and heart disease, were felt to create the least social distance. Cancer is also a hidden disability unless a visible alteration in appearance has occurred as a result of the disease or treatment. Yet it ranked far down at level 10, just slightly above old age, paraplegia, epilepsy, and dwarfism.

Thus, even among a sampling of educated persons, including rehabilitation workers, cancer may be felt to be a disability that sets a person apart. The previous study is evidence that cancer is an ominous label that creates an aura of dread and finality. Its stigma is so indelible that it is not removed even after a patient has been clinically cured. As Dr. Dietz has observed:

This deep-seated fear of cancer has, for a long time, prevented widespread public understanding of the actual potential that exists for cure or long term survival, and the associated rehabilitation now possible. This persists in spite of the survival figure... [for cancer patients] which contrasts strongly with those for patients with stroke and heart disease.... Early death is a common sequella, compared with survival following a diagnosis of cancer. Approximately 50 per cent of those with a history of stroke die within one year, and 35 per cent of those who have suffered coronary occlusion die within one month, including the 15 percent who 'drop dead.' (13)

A factor which may contribute to the public's unshakeable fear of cancer is the persistent though erroneous belief that it is contagious. The theory that the disease could be spread by the transmission of a parasitic microorganism is the oldest hypothesis of the origin of cancer. (14) Originating in ancient history, the theory continued throughout the Middle Ages and reached the height of its popularity around the turn of this century. (15, 16) Though the scientific consensus had shifted to a non-infectious concept of cancer as early as 1910 (17), the seeds of the theory had been sown. As a result, the cancer patient of today must continue to reap the bitter harvest of such outmoded opinion on often unexpected occasions. (See the discussion of employers' attitudes, infra.)

The repercussions of having been treated for cancer extend to the economic sphere as well. A return to a useful vocation is often necessary to the restoration of self-esteem and ego-strength that is part of the rehabilitative process. Yet the patient who has won the fight against cancer may find himself or herself confronted by a new battle on the employment front. This was among the conclusions of a recent study for the California Division of the American Cancer

Society by Professor Frances Feldman of the University of Southern California School of Social Work. (18) The 92 participants in the study, all of whom were clinically cured of either breast, head/neck, or colo-rectal cancer, were randomly selected from the data compiled by the Los Angeles County Cancer Surveillance Program. The sample of patients met the following criteria (19):

Working at the time of diagnosis (pragmatic evidence of employability at that critical juncture);

Twenty-five to 50 years of age at the time of diagnosis (and so presumably having accrued qualifying work experience and/or probably facing at least 10 more years of work under ordinary circumstances);

In one of 6 occupational groups calling for some education or training, whether preliminary to or on the job (thereby offering the employer a certain level of marketable knowledge or skill). Using the U.S. Bureau of Census occupational classifications, the selected occupations included registered nurses, teachers, managers, retail sales clerks, bookkeepers, and secretaries; and

Residing in the Los Angeles metropolitan area.

Another criterion was that the diagnosis would have been reached sufficiently long ago to have offered time in which the respondent could have had subsequent experience in working or seeking work, but not so long as to preclude use by an employer or potential employer of the 'five year cure' or 'symptom-free' tactic (i.e., requiring that the person applying for the job be without evidence of disease five years after diagnosis or treatment.) (20)

At the time of the interviews, nearly 90 percent of the sample were employed full or part time; 88 percent had remained in the



occupations they had followed for many years, and 71 percent were still with the pre-cancer employer nearly three years after the cancer diagnosis with some advances in salary and position. (21) They continued to perform tasks normal to their occupations despite a medical history that might suggest reduced ability to carry out certain functions. (22) The majority had only one absence from work, and this was at the time of diagnosis. Only 17 percent were absent subsequently because of the cancer or its treatment, and generally only once. (23) Most respondents also continued to have the same group health insurance and fringe benefits as other employees in the same work establishment. (24)

However, of the 29 percent who were no longer with the pre-cancer employer, seven persons (9 percent of the total sample) had either been dismissed or "pressured" into leaving because of their respective health histories. (25) (Those persons had been with the pre-cancer employer for periods ranging from one month to 20 years.) Seventeen respondents (19 percent) reported that working conditions or salary levels had been adversely affected by their health histories; 5 percent of those still employed (whether or not by the pre-cancer employer) found themselves with either no group health care coverage or reduced coverage, and 8 percent were ineligible for any or for increased group life insurance coverage. Whether currently unemployed or employed in the pre-cancer establishment or in another job, 24 individuals (26 percent) had sought work after the cancer diagnosis. (26) Twenty persons (22 percent) had been rejected at least once (some, many times) because of their cancer history. (27)

(Some of the employers' responses were: insurance premiums for all employees would be raised, risk of absenteeism would be increased because of later illness, "We're too small to absorb someone with such a serious problem," and "Come back when five years have passed."

(28) In an incident which was a throwback to the once prevalent view that cancer is contagious, one respondent at a public employment placement office reported that "the employment interviewer asked me to exchange the pen with which I was filling in an application for a pencil; pencils are cheaper to discard." (29)

Though 71 percent of the respondents were still with their pre-cancer employers, a fourth of these believed they were the objects of negative attitudes or of outright discrimination at work. In 12 instances of cancer-related changes, a third (four persons) were the result of overt hostility expressed by fellow workers or were changes in work location specifically designed to force the former patient to leave. (30) Another 13 persons (14 percent of the sample) received no salary advances at times when other employees received them. (31)

Patients who changed jobs after they had been cured reported exclusion from group health or life or disability insurance programs. (32) Some patients changed occupations because of their inability to find work in their own fields. For example, one accountant became a bartender in a friend's business. (33)

According to the study, "the clues...suggest that some overt and covert discrimination does exist: in the work setting, in the market place where the former patient seeks to reenter the work

force, and in certain conditions presumably externally imposed on employers and potential employers." (34) This situation exists despite the fact that the 1975-76 California legislature amended the state's fair employment practices legislation to prohibit employment discrimination because of a person's "medical condition," i.e., "any health impairment related to or associated with a diagnosis of cancer, for which a person has been rehabilitated or cured, based on competent medical evidence." (35) Indeed, the fact that the California legislation, introduced by the late Assemblyman Alfred C. Siegler, is unique in the United States reflects the historical inattention to job discrimination and other social problems that beset cancer patients.

It is apparent that the remedies for those problems are not only legal in nature. Among other measures the American Cancer Society study recommended are extensive educational efforts aimed at the public, especially employers, to dispel the stereotypes and myths on which such discrimination is based. (For example, the study recommends an attack on the common perception of cancer as contagious by clarifying publicly the implications of using the term "virus" in cancer research.) (36)

#### In the Isolation Ward: Medical Considerations

The field of rehabilitation medicine is very new. It originated in World War II, when sizeable numbers of the military were maimed functionally and psychologically. (37) Led by Dr. Howard Rusk, the field has slowly acquired trained disciples. (38) Most of the medical and paramedical personnel entering rehabilitation medicine have

concentrated on the needs of persons with spinal cord injuries, diabetes, or stroke. In this respect, the cancer patient has been the victim of neglect.

Among the factors that make rehabilitation more difficult for the cancer patient one does not expect to find the attitudes of the medical profession itself. Nevertheless, the responses of physicians and rehabilitation personnel have aggravated the problems of the potential rehabilitant. According to Dr. Healy,

Unfortunately, physicians also maintain a pessimistic attitude toward rehabilitation of the cancer patient. This feeling is due to several factors in the physician's education. He is given very poor exposure to cancer in his medical curriculum. What the medical student does get is fragmentary, i.e., each specialty group will discuss cancer as it affects a specific anatomic site. The cancer patient to whom a student is exposed is usually an advanced or terminal case. Rehabilitation is not even considered, let alone discussed with the student. There is rarely an attempt to present to him the basic concepts of oncology. The medical student's exposure to the basic concepts of rehabilitation is even more lacking. Rehabilitation medicine is unfortunately equated by the physician to physical medicine. Whatever term is used it is merely an elective for the student and rarely elected. As a result, the average practicing physician has little knowledge as to what rehabilitation is all about.

The paramedical groups also have the same fatalistic attitude regarding cancer that any lay person possesses but in addition they are exposed to the pessimism of the physicians with whom they associate. This results in even greater pessimism in this group. We have had a great deal of difficulty in the past years recruiting physical and occupational therapists. (39)

Another factor that complicates the task of effective rehabilitation may have its genesis as far back as the time when the diagnosis



is given to the patient. Dr. Melvin J. Krant, Chairman of the University of Massachusetts School of Medicine, has observed,

One of the overriding problems...for the physician addressing the cancer patient is that he is cast in the role of condemner of the flesh and spirit, and ultimately executioner, when he gives the diagnosis of the disease to the patient .... He looks upon himself, and may be looked upon, as being the creator of the event rather than merely its reporter. If, in addition, the physician's attitude toward that cancer...is one of fatalism and futility, then this guilt in being the condemner may easily interfere with his ability to order a logical course of treatment and management. A sense of hopelessness prevails, fostering a feeling of defeat and inevitability in both the patient and the physician.... A physician unfettered by guilt, or one who sees his role as one of caring rather than curing, is in a better position to support a patient through a logical system of planned actions. (40)

The historic approach to rehabilitation has been to refrain from beginning any program until treatment is over and only the disability is left. (41) However, according to Dr. Dietz, this is often much too late: "The sooner such rehabilitation efforts are set in motion, the more effective ultimate rehabilitation is likely to be." (42)

In the previous section of this chapter, some of the general social, economic, and psychological problems of the cancer patient have been considered. In the next section, the focus will shift to the specific rehabilitation problems of patients who have had head and neck, breast, and colo-rectal cancer.

## II. Specific Needs of the Cancer Patient

### Head and Neck Cancer

While head and neck cancer includes malignancies at any of numerous sites (e.g., larynx, skin, nasal, oral or pharyngeal cavities, paranasal sinuses, salivary glands, etc.), it has been observed that this type of cancer is generally the most mutilating kind. (43) Treatment may consist of surgery, irradiation, or a combination of both. (44) Head and neck cancer patients as a group are good candidates for rehabilitation because they have a better long-term survival rate than patients with other types of cancer. (45) Unfortunately, however, many of the necessary curative and palliative procedures result in either severe cosmetic or functional defects that may impair the rehabilitative potential of these patients. (46)

#### Functional Defects

For example, radical surgical procedures to eliminate head and neck cancer may require the impairment or sacrifice of vital organs. The resulting functional defect may be more distressing than the cosmetic repercussions. (47) Radical surgery of the nasal cavity may impair the sense of smell. Various oral surgical procedures may create difficulties with mastication. Cancer of the maxillary sinus may require enucleation of the eye ball, resulting in blindness. (48) But it is the removal of the larynx, which results in complete loss of speech, that has been the object of the greatest attention. Members of the 1967 interdisciplinary conference on head and neck cancer found that "Rehabilitation of the laryngectomized patient is

probably the only rehabilitative problem of the cancer patient that... has received research and training grants in the hope of relieving this situation." (49)

About 2,500 to 4,000 laryngectomies are performed annually in this country, and there are approximately 25,000 laryngectomees alive in America today. (50) Those stricken are usually in the 50-70 year age range and are nine times more likely to be men than women. (51) Since the incidence of laryngectomy and the survival rate of laryngectomees is increasing, while at the same time the average age of the laryngectomy patient is declining, there will be an increasing number of candidates for rehabilitation in this area. (52)

Four modes of communication are open to the laryngectomee. He may use hand signals, communicate by writing, use an artificial larynx, or learn esophageal speech. (53) Though hand signals and writing are considered only temporary measures, it has been estimated that nearly a third of all laryngectomees continue these methods for the rest of their lives. (54)

Esophageal speech, which is generally encouraged by most physicians, is formed by taking air into the mouth and pushing it with the tongue or muscles of the pharynx into the esophagus. As air is expelled upwards, words are formed by the articulating organs of the oral cavity. (55) While laryngectomees communicated primarily with the use of instruments in the 19th century, a few physicians of that period reported isolated instances in which their patients spontaneously developed esophageal voice. (56) Communication by this method became more frequent as improvements in surgery led to longer survival for laryngectomees. (57) In 1908 a German physician

named Gutzmann astonished the medical world by reporting that he had successfully taught esophageal speech to 25 laryngectomees. (58, 59) By 1919, the term esophageal speech had been introduced by another European physician, Seeman, at the meeting of the Laryngological Society in Vienna. (60)

Mortality rates for laryngeal cancer dropped dramatically as a result of improved surgical procedures in the 1920s and the development and use of antibiotics in the late 1930s. (61) As a result, many more laryngectomees were surviving their surgery and were thus able to communicate by means of esophageal speech or artificial devices. (62)

About two-thirds of all laryngectomees are able to acquire esophageal speech, although only about half learn to speak fluently. (63) Apparently, there is "complete disagreement" among surgeons about the appropriate time to begin esophageal speech therapy. (64) Some feel that preoperative visits by a speech therapist or a laryngectomee well trained in esophageal speech can facilitate early rehabilitation. Other surgeons are opposed to such early therapy. Several physicians especially objected to the visit by the laryngectomee, which has been known to trigger preoperative psychological problems. (65) Motivation has been cited as the most important factor in learning esophageal speech. (66, 67) However, other factors such as the extent of the patient's surgery, the effects of preoperative or postoperative radiation, hearing loss, the patient's generally poor physical health and/or the presence of distant metastases may inhibit the development of esophageal speech.

The fourth mode of speech is via artificial larynx (the electro-larynx). The earliest precursor of the electric model was the reed-type vibrator devised by the laryngologist Czermak and a scientist



named Brucke in Germany in 1859. (68) (This was 18 years after the first reported instance of esophageal speech.) (69) Refinements in the construction of such devices continued as surgical procedures became more advanced. (70) By 1942 the first successful electro-larynx had been developed by J. Greene and G. Wright and sold by the Aurex Corporation. (71) A later variation of the electro-larynx was introduced in 1950 by the Bell Telephone Company. (72) The device is placed against the neck and sound waves are then transmitted through the neck to the oral cavity. (73) However, the electronic device also has several disadvantages: it requires the use of one hand, produces a continuous buzzing sound during speech (which thus has a very mechanical sound), and draws attention to the person's condition. (74)

According to Dr. Daniel H. Zwitman, Assistant Professor of Surgery in the Head and Neck Division at UCLA and Director of the UCLA Speech Clinic, there is a tremendous need for an intraoral electro-larynx that can be concealed within the mouth and has good tonal quality. (75) Unlike the hearing aid, which has become increasingly more sophisticated over the years, the development of the artificial larynx has not progressed since the 1950s. (76) This may be attributed to the fact that there is a comparatively limited market for the artificial larynx in contrast to that for the hearing aid. However, Dr. Zwitman, in conjunction with Dr. John Beumer of the UCLA Dental School and Professor Siegfried Knorr of the UCLA Department of Engineering, is currently developing an intraoral electro-larynx which is expected to be available to consumers in 1977. (77)

## Psycho-social Problems

Because of its often mutilating effect, head and neck cancer poses a tremendous emotional threat to the patient and his family.

(78) In the words of A. Beatrix Cobb, Ph.D., former head of the Medical Psychology Section at M.D. Anderson Hospital:

Despite giant strides in the areas of plastic surgery and prosthetics, the disfigurement is still grossly apparent. It is traumatic to experience mutilation of the body image by loss of a limb, but to endure the agony of a face made grotesque to the point that even friends and family members avert their eyes while speaking with the patient; or betray repulsion in other ways, is excruciating punishment. To live with the knowledge of the presence of foul odors arising from some of the fulminating tumors, and to realize how abhorrent the smell is to others is another step into emotional hell. To lose the ability to speak and to be forced to communicate in a 'Donald Duck' type esophageal speech is psychologically offensive, especially to younger women. The patient needs and deserves the unconditional regard and emotional support of the entire medical team (including an empathetic psychiatrist or psychologist), as well as the encouragement of a loving and understanding family. (79)

But with the exception of programs at a few institutions, the medical profession has not yet recognized the need for a multidisciplinary group of trained professionals to meet the psychological, social, and vocational rehabilitation needs of the patient. As the 1967 head and neck cancer conference revealed, "It was obvious that at the institutions represented at this conference a true inter-disciplinary rehabilitation team approach was not being utilized and, in fact, was not deemed necessary. Aside from the active participation of the attending physician and nurse, other disciplines were not called

upon unless the individual case required their participation." (80)

It is apparent that the focus of physicians has been on the successful diagnosis and treatment of physical problems. Three-year and five-year survival rates are the kinds of quantitative measurements traditionally employed. There has been little attention paid to the quality of life following treatment of these patients. At the 1967 conference, "it was pointed out that of the thousands of head and neck cases treated each day, no one really knows what happens to them. Are they being hidden in cellars or do they become a part of the community? Is the patient happy in his role?" (81)

A subsequent study at the University of Pennsylvania and Pennsylvania State University provided some discouraging answers. Researchers followed the adjustment of 50 maxillofacial cancer patients; the average length of time that had elapsed following treatment was 3.75 years. The overall finding of the study was that 44 percent of all patients surveyed displayed a poor long-term adjustment in the areas of either work, social, or sexual functioning. (82) Reduced heterosexual functioning was the most dramatic finding here: of the 38 patients who had been sexually active prior to illness, 34 percent had markedly reduced their activities following treatment. (83) The authors concluded that "treatment solely directed at the patients' malignancies, no matter how effectively accomplished, may not be sufficient to meet their overall needs. The total psychological adjustment must also be considered, if the beneficial effects produced by surgery or radiation are to be translated into a maximal rehabilitative outcome." (84)

Apparently, the rehabilitation potential of head and neck cancer patients is not being fulfilled. Unfortunately, the disregard for the needs of the total patient occurs not only with this type of cancer but with other types as well.

### Breast Cancer

Breast cancer is the most common type of cancer in women today. (85) When found early enough, the survival rate is as high as 85-90 percent. (86) Therefore, assuming prompt and effective treatment, usually by mastectomy with or without radiation therapy, the breast cancer patient is a good candidate for rehabilitation. As in the case of head and neck cancer patients, rehabilitation problems have both physical and psychological dimensions.

#### Physical Problems

While the majority of mastectomy patients experience a degree of arm edema on the operated side, the swelling that occurs in the postoperative period subsides in most cases. (87) However, in a significant number of women, swelling may occur weeks or months after surgery and may persist. (88) Lymphedema disability then becomes a rehabilitation problem which is proportionate to the extent of the edema and the disfigurement it creates. (89) Because of the resulting restriction of shoulder motion, the weight of the extremity, and the pain involved, lymphedema can create vocational, emotional, and economic problems for the patient, the impact of which may be felt by her family. (90)



Why one woman develops lymphedema and another woman given identical treatment does not is considered an enigma. (91) But in a recent study of 271 women followed prospectively from one to four years after treatment for breast cancer at M.D. Anderson Hospital, as many as 108 (40 percent) developed some degree of lymphedema. Of those women, 38 (35 percent) manifested severe lymphedema. (92) The study indicated that while lymphedema occurs more frequently in women treated by a radical mastectomy (50 percent with or without radiation), it also occurred in patients treated by a modified radical (37 percent), simple mastectomy (27 percent), and irradiation alone (19.5 percent). (92) However, it was noted that the incidence of lymphedema was 55 percent in women who received no post-operative physical therapy compared to the 33 percent for women who followed a post-treatment therapy program. (94)

Whatever the cause of lymphedema, the condition must be recognized in its early stage so that remedial measures (range of motion exercises, pneumomassage, or possible surgical intervention) may be instituted. (95) According to Dr. Healey, "almost invariably" women are told that the condition is a normal sequel of the operation and that they must live with it. (96) However, nothing could be worse than exposing a woman to such a defeatist attitude. (97)

Another common problem that may impede the physical rehabilitation of the mastectomee is shoulder dysfunction, which may occur after treatment by simple mastectomy or radiation alone, as well as after radical mastectomy. (98)

Shoulder dysfunction results from the lack of proper immediate postoperative rehabilitation care. The blame for this lack of proper continuity of care rests primarily upon the attending physician. Instructions to the patient by the surgeon are usually very nebulous, epitomized by such statements as 'Don't baby your arm, use it any way you want.' Other cliches are 'Comb your hair, hook your bra,' etc. (99)

Instead of giving such vague directions, the physician should institute a full range of shoulder activity motion. Such a regime is best managed under the supervised direction of physical therapists. (100) But where such services are unavailable, efforts must be made to educate physicians about effective post-operative care of breast cancer patients. (101)

It should be noted that in some cases shoulder dysfunction problems result from the patient's lack of motivation and her wish to draw sympathy to herself. (102) Such emotional problems may indicate the need for psychological as well as physical care as part of the program of rehabilitation. (See discussion, infra.)

A third problem--finding an appropriate prosthesis--has been solved as a result of the proliferation of breast prostheses in the past decade. According to Mrs. Terese Lasser, who originated the Reach to Recovery Program (see discussion below), there are enough varieties of prostheses to suit the needs of almost every woman who has had a mastectomy, as long as she is willing to take the time to shop for the one that is right for her. (103) Because of the pressure exerted by women in general and the Reach to Recovery Program in particular, many types of prostheses--e.g., air and fluid filled plastic, silicone gel filled and custom-made models--

have been developed by the persons who are more often "consumers" of these products than professional prosthetists. (104) While some custom-made models may cost over \$360, Mrs. Lasser has indicated that the most expensive prosthesis is not necessarily the best one for a particular woman. (105) The most popular prosthesis is a \$50 liquid-filled plastic model. (106) Information on all available prostheses and how to obtain them is available from the Reach to Recovery Program of the American Cancer Society.

### Psychological Problems

As observed at a 1970 rehabilitation conference at M.D. Anderson Hospital, "To save a woman by surgical intervention and then to deny her the emotional support necessary to form a different life style and accept an altered body image is a contradiction in terms." (107)

According to Dr. William M. Markel, Vice-President for Service and Rehabilitation of the American Cancer Society, rehabilitation should begin when the diagnosis of breast cancer is made. (108)

Preoperative emotional preparation can be tremendously important, but the time sequence in the treatment of breast cancer frequently does not lend itself well to this. The time interval from the detection of the mass until biopsy and then the operation may be a matter of hours, or at most several days. Because of this time factor, or for whatever reason, whether the patient has not heard, or whether the surgeon has not really discussed the severity of the problem and the magnitude of the treatment, we find that immediately postoperatively the patient is troubled and has been shocked by the procedure. She may be angry and she is certainly frightened and almost always depressed. (109)

Recently, much controversy (110) has surrounded the single-stage procedure in which a woman is admitted to a hospital for a biopsy and later awakens from the general anesthetic to find that she has had one or both of her breasts removed. According to psychologist Joseph Cullen, Deputy Director of the UCLA Cancer Center, such a single stage procedure may have a "tremendous psychological impact" (111) despite the fact that before surgery the woman was alerted to the possibility that she might have a mastectomy. It has been suggested (112, 113) that even a brief period between biopsy and mastectomy might result in less physical and emotional trauma and facilitate rehabilitation, since it would give the woman time to accept the diagnosis and begin adjusting to its consequences. From the surgical standpoint, a two-stage procedure is also feasible. In a recent study (114), Dr. John R. Benfield, Chief of the Division of Thoracic Surgery at Harbor General Hospital, proved that "an experienced surgeon can recognize the likelihood of cancer in women with breast masses with sufficient accuracy to justify the preferential use of local anesthesia for biopsy when the mass seems likely to be benign." (115) Dr. Benfield concluded,

There is no justification for maintaining the traditional approach of a one-stage procedure under general anesthesia for those women in whom the breast mass is probably benign. These women should be spared the anguish of uncertainty--an uncertainty made more emphatic when previous consent to proceed with mastectomy has been granted. Intuition to the contrary, there is no evidence that cancers treated by the traditional one-stage approach are more likely to be cured than those resected adequately within a few days of diagnosis. (116)



Whether the surgical procedure is done in one or two stages, there are certain psychological problems that plague the majority of post-mastectomy patients (117):

1. Acceptance of a new self-image after the loss of a part of the body.
2. Reluctance to tell others--friends, neighbors, perhaps even family members--about the mastectomy because of embarrassment;
3. Feelings of physical unattractiveness which may prevent or impair relationships with men;
4. Anxieties about recurrence of disease or possible death from cancer.

Dr. John Healey has stated that the attending physician is "morally obligated" to discuss with the patient her family's reaction, sexual adjustment, future motherhood, clothing, breast prostheses, and other issues. (118) However, too often a surgeon for various reasons fails to deal with such matters and leaves the patient to solve these problems for herself. (119)

There has been increasing recognition that the emotional needs of the mastectomee have generally been neglected. Dr. Cullen has observed that the persons interested in the psycho-social aspects of breast cancer are the psychologists and paramedics, not the "power people," who are the physicians. (120) Dr. Melvin J. Krant has also focused on the parochial attitudes that often characterize the surgeon:

The surgeon or radiotherapist is often not the condemner--he is the rescuer. The more evil the condition, the more powerful the rescuer feels.... It is no wonder that a surgeon can justify radical surgery in the name of rescue, and feel totally justified in demanding the patient's gratitude rather than see himself as the initiator of a new set of psychological problems.

Clearly, there are many such individuals in surgery, and even in radiotherapy, who proclaim their omnipotence through their rescue efforts and who do not deign to recognize the new set of problems that emerge as a result of their work. Moreover, why should such powerful individuals pay attention to the quibblings of other human beings, such as nurses, social workers, and especially psychiatrists and psychologists, who from sheer malevolence wish to indict the heroes? Here again...standard medical education fosters this alienation by presenting cancer as a surgical disorder rather than as a multifaceted problem. It discourages the young surgeon from a creative approach to the understanding of his own needs as well as those produced by cancer and cancer therapy. The heroic position does not take challenge well. (121)

The apparent paucity of creative approaches to cancer therapy indicates that the surgeon cannot alone fulfill all of the patients' needs. Therefore, there must be a recognition of the value of the services rendered by other professionals and a utilization of those services by the physician; he must familiarize himself with all available resources and look toward a program of rehabilitation for a woman that extends beyond her discharge from the hospital. (122) At Memorial Hospital for Cancer and Allied Diseases in New York City, a revolutionary group program has been offered since 1970 in which mastectomees share each other's experiences as well as the services of a nurse, social worker, physical therapist, and a Reach to Recovery volunteer. (123) (Reach to Recovery will be discussed infra.) Indicative of the professional resistance historically present, it should be noted that it took time to overcome the reservations physicians had about the value of the team approach before full recognition was given to the efficacy of the program. (124)

Increased attention has also been focused on the quality of life of the breast cancer patient. Two studies, one by the Connecticut State Department of Health (125) and the other at Memorial Hospital for Cancer and Allied Diseases in New York (126), have evaluated the quality of survival of women who have undergone radical mastectomies. (A follow-up of the Memorial study was scheduled for completion in early 1977.) (127) In the past few years, the issue of qualitative survival has been stressed by the Commission on Cancer of the American College of Surgeons, which had planned by January, 1973, to make qualitative assessment a requirement for the College's approval of hospital cancer registries. (128) While it subsequently determined that such a requirement was not feasible because of increased financial burdens that might be incurred at individual institutions, the American College of Surgeons still feels strongly that the quality of survival should be an integral concern of all hospital cancer programs. (129) As a result, some tumor registries, such as the one at Memorial Hospital for Cancer and Allied Diseases, have begun to measure the survival of all of their patients in qualitative as well as quantitative terms. (130)

#### Colo-Rectal Cancer

There are several types of abdominal stomas which may be created as a result of colo-rectal or urologic disease. The ileostomy, more common in younger persons, is associated with ulcerative colitis. (131) A second type of stoma, the ileal conduit, may be created after a total cystectomy as a result of carcinoma of the bladder. (132)

But by far the most common stoma is the colostomy, created after the removal of a portion of the colon. (133) Though cancer of the colon is more common in elderly persons, the number of colostomies done yearly is three times the number of ileostomies and many times the number of ileal conduits. (134) Because the greatest number of new cancer cases (excluding skin cancer) in 1975 (135) was at the colo-rectal site (99,000), the focus of this section will be on the colostomy patient, whose problems are, for the most part, representative of those of ostomates in general.

#### A Dearth of Professional Knowledge

Unfortunately, surgeons, physicians, and nurses admittedly know very little about stoma care or how to learn about it. (136) The surgeon who can create the best stomas does not necessarily know how to care for them postoperatively. (137) During follow-up visits, surgeons are largely concerned with the anatomic patency of the stoma and its physiological functioning. (138) The quality of adjustment the patient has made is seldom investigated. (139) In the opinion of enterostomal therapist Edith Lenneberg and Dr. John Rowbotham, Medical Director of the Stoma Rehabilitation Clinic at New England Deaconess Hospital, "the colostomy patients' recovery to a normal life style is fraught with a great many problems, in that the adaptations that are made by the patients are sometimes most unfortunate and unnecessary;...the cutting off of previous relationships--whether to people or to activities--is very extensive." (140)



Long-term rehabilitation may be complicated by a series of physiological and psychological problems, among them problems with gas and foul odors. The ostomate may experience a deep sense of grief at his loss of anal control, loss of sexual appeal or potency. (141) Since the control of the elimination of body wastes is one of the earliest achievements of an individual, incontinence may imply a return to infancy and helplessness and cause a loss of self-esteem. (142) Despite these seemingly obvious difficulties, according to Edith Lenneberg, psychiatry has been "amazingly disinterested" in the problems of the stoma patient. "We are still in need of additional studies regarding the meaning of the presence of a stoma and bodily wastes on the abdomen." (143)

#### The Enterostomal Therapist

In the past 25 years, the emergence of the enterostomal therapist (ET), who specializes in the care and problems of ostomates, has marked an encouraging development in furtherance of ostomate rehabilitation.

The concept of the ET originated with surgeon Rupert Turnbull of the Cleveland Clinic, where the first formal ET program began in 1961. (144) Since then, nine other training centers have been established--Harrisburg Hospital at Harrisburg, Pennsylvania;\* Roswell Park Memorial Institute at Buffalo, New York;\* Emory University Clinic in Atlanta, Georgia;\*\* Tuscon Medical Center in Arizona;\*

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\* funded initially by the American Cancer Society  
\*\* funded initially by the National Cancer Institute

the San Diego School of Medicine of the University of California;\* M.D. Anderson Hospital in Houston, Texas;\*\* the Midtown Hospital Association (three hospitals) in Denver, Colorado;\* the Boston University School of Nursing in Massachusetts;\*\* and Ferguson-Droste-Ferguson Hospital in Grand Rapids, Michigan (discontinued as of summer, 1976). (145)

According to ET Edith Lenneberg, enterostomal therapy may be "as narrow as knowledge of bags and economic resources or as broad as comprehensive nursing care with exquisite attention to pathologic processes, psychological issues, assessment of the patient's own physical, psychological, and social resources, planning for his optimal functioning in the community, as well as patient teaching."

(146) ETs may be available for in-hospital care, for follow-up visits for six weeks or longer, for lifelong regular checkups, and for crisis intervention. (147) Even as early as the preoperative period, this paramedical specialist may be called in to discuss with the surgeon the best location for the stoma and postsurgical stomal care and appliances. (148) It has been suggested that because of the expertise of the ET, it is expedient for the surgeon to transfer post-operative stomal care of his patient to the therapist, whom he can support with his specialized advice. (149)

While ETs were originally recruited from numerous fields, the majority of those who entered this specialty were registered nurses. (150) As of September, 1976, every candidate for an ET training

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\* funded initially by the American Cancer Society

\*\* funded initially by the National Cancer Institute

program must be a registered nurse. (151) While the number of ETs in the U.S. has increased from 200 (in 1973) to 647 (as of August, 1976) the need for such specialists is still greater than their ranks. (152) In 1975, the International Association of Enterostomal Therapists (the ET professional organization which began in 1968 as the North American Association for Enterostomal Therapy) organized a regional program in the United States to help meet the demand for ETs at the local level. (153)

Despite the need for more training programs, ETs as a group wish to maintain high standards for their specialty. (154) Accordingly, as of 1977, each new ET training program will have to meet the criteria established by a newly formed accreditation committee (composed of physicians, nurse educators, and ETs) which will make on-site visits before each new training program is certified. (155)

### III. Meeting the Rehabilitation Needs of Cancer Patients

#### Making Promises: The Role of the Federal Government

Until the genesis of the National Program for the Conquest of Cancer in 1971, the rehabilitation needs of the cancer patient came primarily within the ambit of the Vocational Rehabilitation Administration (later renamed the Social and Rehabilitative Services Administration and now called the Rehabilitation Services Administration). The initial interest of the federal government in rehabilitation began with the national vocational rehabilitation for disabled World War I veterans. (156) The early programs of the Veterans Administration emphasized prosthetic needs and vocational training rather than the psychological aspects of disability. (157)

The World War II program for veterans incorporated more psychosocial emphasis and defined vocational rehabilitation services as "any services necessary to render a disabled individual fit to engage in a remunerative occupation." (158) Further legislation in 1954 provided federal funds to the states for research, demonstration, and training activities and extended services to disabled civilians. (159, 160)

It was not until 1965 that the cancer patient received special attention. After the report of the President's Commission on Heart Disease, Cancer, and Stroke, Congress made funds available for Regional Medical Programs to expand the education of physicians in these areas and to combat the effects of these diseases. However, only about 7 percent of the RMP funds were actually spent on cancer



projects (161) and the RMPs have since been discontinued. (For a discussion of the genesis and fate of the RMPs, see Book Two, Chapter 7.)

In 1966, after calling a conference of rehabilitation specialists, the late Miss Mary E. Switzer, who was the U.S. Commissioner of Vocational Rehabilitation at that time, launched a concerted effort to help the cancer patient. (162) Prior to this time, a cancer patient could not be accepted by a state rehabilitation agency unless the patient had been free of metastases for at least 18 months after treatment. To change this Miss Switzer issued a directive that the patient could now be accepted at the time of referral regardless of post-treatment time, as long as there was no evidence of metastases. (163) Miss Switzer also succeeded in obtaining more federal funds for research and demonstration and for programs such as regional maxillofacial prosthodontic training centers. (164) At that time she said, "The rehabilitation of cancer patients has priority over almost anything else we are trying to do." (165)

But the promise inherent in Mary Switzer's words was never fulfilled. Under the Rehabilitation Act of 1973, the federal government was authorized to spend a minimum of \$2 million per state in fiscal years 1974 and 1975 under Basic State Grant Programs. (166) Under this system funds are apportioned among the states on the basis of population and income; the federal government assumes 80 percent of expenditures and the state provides 20 percent. (167) But very few cancer patients have actually been rehabilitated under this program. The total number of cancer patients rehabilitated during

the past four years is as follows (168):

1972 .....	1,199
1973 .....	1,216
1974 .....	1,152
1975 .....	1,314

The reasons why so few cancer patients have received these rehabilitation services may be inherent in the rehabilitation legislation itself. Under Section Two of the Rehabilitation Act of 1973, as amended in 1974, the purpose of the program is to provide services for handicapped individuals, "serving first those with the most severe handicaps, so that they may prepare for and engage in gainful employment...." (169) While section 7 (13) of the Act defines "severe handicap" as "the disability which requires multiple services over an extended period of time and results from amputation, blindness, cancer, cerebral palsy..." and a list of other diseases, the only specifically cancer related disabilities categorized as "severe" in a recent statistical survey by the RSA (170) were laryngectomies and leukemia.

Under this legislation, numerous cancer patients may not qualify for RSA services. Rehabilitation is aimed at "gainful employment" (including homemaking), which precludes services for any cancer patient who is retired. In addition, the rehabilitation problems of certain cancer patients may not be considered a "severe handicap." Note the absence of mastectomees and ostomates on the list of severe disabilities. Finally, some cancer patients may have problems (e.g., psychological, social, cosmetic) which are not serious obstacles to

gainful employment but which nevertheless interfere with successful readjustment to a normal life. None of these individuals would be eligible for RSA services, either. This may explain why so few cancer patients have been aided by the efforts of this branch of the government. The federal cancer control program ignored developing demonstration projects in continuing care and rehabilitation until the mid 1960s. (171) Then, professional education of physicians and dentists in head, neck, and oral cancer detection and management was funded through several demonstration projects. (172) Two maxillofacial prosthodontists training programs were established, providing the small national pool of such specialists until very recently. (173) Continuing professional educational materials for physicians and nurses, supported by the Cancer Control Branch, did emphasize the continuing needs of cancer patients and their families. But the overall concern was passive rather than active. (In 1961, New York University received a community demonstration grant of about \$50,000 a year for "rehabilitation," but no program description was available to learn what this project was to accomplish.) (174)

Intensified interest in solving the cancer problem led to the inception of the National Program for the Conquest of Cancer in 1971. One product of the National Cancer Program Strategic Planning Sessions (October 1971 - March 1972) was the formulation of a list of objectives to be accomplished by the federal government. (175) The seventh of these was to "develop the means to improve the rehabilitation of cancer patients." (176) In December, 1972, the National Cancer Rehabilitation Planning Conference met to define specific projects through which

Objective Seven could be implemented. The Conference recommended three approaches (177):

- (1) Development of the national capability to provide rehabilitation to all cancer patients. Suggested means to this end were increased availability of rehabilitation services, the education of health professionals, public education of health professionals, public education and community involvement, and third party assistance.
- (2) Development of improved means to restore maximum physical and functional capabilities to cancer patients. Suggested were improved physical restorative services, increased palliative and supportive care and services, and improved prosthetic and orthotic devices.
- (3) Development of improved means to restore the cancer patient's life style and reinforce reentry into the community. This would involve additional psychosocial and vocational emphasis.

While the goals enumerated above were a project of the National Program for the Conquest of Cancer of the 1970s, they may be characterized as the proverbial new wine in old bottles. In 1956 the Commission on Chronic Illness, created by the American Medical Association, the American Hospital Association, and the American Public Welfare Association, published the findings of its seven-year study of chronic illness in America. (178) Among its recommendations in



the field of rehabilitation were the following:

Physicians...must equip themselves with knowledge of new methods of treating long-term illness; learn to use other health professions in care of the patient, and become familiar with community resources that...the patient may require. (179)

Training and recruitment programs to alleviate current shortages and to avoid even more serious future deficits must be built upon...the Commission's primary objective: a dynamic approach to chronic illness that will prevent such long-term disability, minimize its effects, and restore many of the disabled to a useful and productive place in the community. (180)

Vigorous and more effective public education is needed...to bring about the needed reforms. (181)

Demonstration projects and special follow-up studies should be directed toward analysis and evaluation of the effectiveness of various methods of treatment and rehabilitation and the subsequent status of patients with respect to their capacities for self-support and self-care. (182)

#### Filling the Void: The Role of Volunteer Organizations

When the needs of the cancer patient are not met by his physicians or public programs, the patient must contend with his problems by himself. The impetus for the organization of most community rehabilitation programs and organizations has evolved not from professionals but from lay persons who have felt the impact of a medical problem on their lives and have had to cope with it in a novel way. (See especially the early history of the National Tuberculosis Association, the Red Cross, and the National Association for Crippled Children and Adults in Chapter VI of A History of Vocational Rehabilitation in America by C. Esco Obermann, 1965.)

Volunteer assistance to the cancer patient has emerged in the same way. Groups such as Reach to Recovery, ostomy and laryngectomy clubs, have reflected, according to one writer, not only "generosity of spirit, but have represented a contribution to human welfare by people who have themselves experienced the anguish of having been victims of cancer." (183)

It has only been after the initial pioneering efforts of such assertive individuals that larger, more powerful organizations such as the American Cancer Society have endorsed such programs. (184) The ACS, perhaps the most active sponsor of voluntary programs, has become increasingly aware of cancer rehabilitation needs only since the 1960s. (185) One reason offered for ACS' late recognition of this area has been that until survival rates had improved for cancer patients, there was no perception of a need for organized rehabilitation efforts. (186) Another explanation has been given by Dr. William Markel:

The real problem in this area has been getting the acceptance of the medical profession that these people need rehabilitation.... I don't think doing the rehabilitation is [a problem]. We have always managed to do what has to be done once we recognized that there is a need. But we can be awfully slow at recognizing the need or changing the philosophy. The medical profession is probably worse than most.... Many doctors send their patients right through, send them home without even going through the rehabilitation process. (187)

One of the most successful rehabilitation service programs of the ACS has been Reach to Recovery for mastectomees. The need for the program has been created, again, by the narrow view of medical treatment common to many physicians. As Dr. Markel has observed, doctors

see a therapeutic success after removing a cancer. But "the woman says, 'What I'm going to worry about now is will my husband love me and how am I going to look?' She's dealing with a day by day problem, not survival rate. Doctors haven't appreciated that." (188)

Reach to Recovery is designed to deal with the day to day reality of the woman who has had a mastectomy. The program began in 1952 after Mrs. Terese Lasser underwent a mastectomy and discovered the acute lack of information and support available to a woman to help her cope with her postoperative questions and fears. (189) Inspired by the self-help model of Alcoholics Anonymous, Mrs. Lasser began a program in which a mastectomy patient, with the consent of her physician, is visited by a volunteer who has had a mastectomy herself. The visitor gives the woman a free Reach to Recovery kit, which contains an information manual, equipment for exercises (which are not begun without the surgeon's approval) and a temporary prosthesis for the patient to wear while she is in the hospital and until she is able to wear a more permanent one. The volunteer may suggest various clothing adjustments and may answer whatever non-medical questions the patient asks. (190)

Mrs. Lasser recalls that she began making hospital visits to women who had had mastectomies at the request of her own breast surgeon. "He asked me to see one of his patients. Then the woman in the next bed wanted to see me and the woman in the next bed after that" and the need for such a service became apparent to her. (191) Though Mrs. Lasser had approached the American Cancer Society several times about sponsoring her program, it was not until 1969 that ACS

came to her and offered her their sponsorship. Since then, Dr. Markel has indicated that the program has become "tremendously important." With 1,080 volunteers, it is now the largest self-help program for women in the United States. (192) He attributes much of its success to the quality control of its volunteers on which Mrs. Lasser and the ACS have always insisted. (193) A Reach to Recovery volunteer must have the certification of her own doctor that she is psychologically suited for her role. She is then fully trained and certified before she is allowed to begin visits. (194) She is also periodically recertified and reevaluated. (195) Dr. Markel says,

I think the big bang in Reach to Recovery is when the patient in the bed looks up and a woman comes through the door. (And we insist [that she] wear a tight fitting gown so that both breasts show and her hair is all combed.) We think we've made it then at that point. She looks up. You are a Reach to Recovery volunteer and you've had a mastectomy. If something clicks here, then all the rest of it is not terribly important, because then she wants to get well. (196)

A criticism leveled at the Reach to Recovery program has been its stipulation that a volunteer cannot visit a patient unless the surgeon requests the visit. Dr. Markel feels that such a requirement is not unreasonable since the surgeon is ultimately responsible for the patient's welfare. (197) For the most part, this program has been accepted by the medical profession. (198) Dr. Markel has indicated that there are now many hospitals where a visit by a Reach to Recovery volunteer is automatic unless the physician writes an order expressly forbidding it. (199) According to Mrs. Lasser, the Reach to Recovery program will soon include seminars for the



teenaged sons and daughters of mastectomy patients. (200)

The first move made by ACS in the direction of organized rehabilitation services was its sponsorship of the International Association of Laryngectomees (IAL), founded in 1952. (201) As of 1973, IAL included 190 affiliates from 43 states and 11 foreign countries. (202) The purpose of the program is "to promote and support the total rehabilitation of laryngectomized persons by the exchange and dissemination of ideas and information to the clubs and to the public, to facilitate the formation of new clubs, to foster improvement in laryngectomee programs, and to work towards the establishment of minimum standards for teachers of postlaryngectomy speech." (203) In much the same manner as the Reach to Recovery program, IAL, upon request of the patient's surgeon, will send a well-rehabilitated volunteer to visit the laryngectomee and to answer non-medical questions and offer emotional support. (204) According to Dr. Markel, these visits may be crucial since "one of the big [rehabilitation] problems is [that] if the patient gives up, he'll never learn. But if someone can talk to him, maybe he will try." (205)

Among the programs of the IAL are seminars and institutes for prospective speech therapists, public and professional education in first aid and artificial respiration required for laryngectomees, a registry of laryngectomy speech instructors, international annual meetings, and job market education to help overcome employer discrimination against laryngectomees. (206)

The ACS also sponsors a Colostomy Rehabilitation Program, which has a volunteer visitor program similar to that of IAL and Reach to Recovery. This ACS program is not as broad as the other two programs, however, because ACS works in such close cooperation with the independent United Ostomy Association (UOA) (see below). The ACS philosophy differs from that of UOA in that ACS does not believe in the club principle: "We don't want colostomates making a social life out of being colostomates. The UOA has membership drives; we don't want membership drives. We want people leaving us." (207)

Dr. Markel also feels that the enterostomal therapist has "absolutely changed the complexion" of stoma management:

The ETs have done such a great job that it's hard for me to get unhappy that we haven't developed the same kind of volunteer program. I don't think I have a right to say it has to be done our way through volunteers. If the patients come out of the hospital now and there is a mechanism for rehabilitating them and they can go to work, that's it. If NCI does it, or the UOA does it, or Blue Cross does it, I don't care. Our job is to get it done. And then go on to something else with our money. We are encouraging our divisions to develop visitors. But we are pressing very hard on the ETs because to me that looks like the way to go. (208)

#### IV. Rehabilitation in Perspective

While rehabilitation may be considered the fourth phase of medicine, we have seen in the preceding chapter that it is undoubtedly the most neglected phase. Most of the efforts that have been made in this area have focused on quantitative rather than qualitative success. In addition to these general factors, there are also some more specific observations:

--Improved survival rates and the activities of self-help groups such as Reach to Recovery, laryngectomy and ostomy clubs have led to a more hopeful outlook for the rehabilitation of the cancer patient. However, there is still a need for the medical profession to modify its predominantly pessimistic attitude toward this field of medicine. This may be accomplished in part by including a creative, multi-faceted approach to cancer rehabilitation in medical school curricula. In addition, the outlook of physicians who are already in practice, particularly in smaller communities, may improve if they are fully informed of the entire range of rehabilitation services available to their cancer patients.

--While training programs for paramedical specialists such as the ET have expanded in recent years, they must continue to proliferate in the future if prospective rehabilitation needs are to be met. There must also be acceptance by physicians of the important function which these paramedics serve in a multi-disciplinary team approach to rehabilitation.

--The quality of survival of the cancer patient is an issue which has recently received increased attention from the American College of Surgeons in their evaluation of tumor registries. However, while the quality of life has generated interest in the areas of policy-making and research, this concern must be demonstrated by more surgeons and other physicians in their respective individual relationships with their patients. In particular, there must be a greater awareness of the psycho-social problems of the patient and his family.

--While advances have been made in some areas of prosthetics (e.g., the breast prosthesis), commercial considerations have inhibited the development of other aids to rehabilitation such as the artificial larynx. The increased availability of financial support from private and governmental sources would give added impetus to research into the improvement of such devices.

--As noted in this chapter, several conferences on rehabilitation have been held in recent years. Undoubtedly, interdisciplinary panels of physicians, paramedics, social workers, psychiatrists, psychologists, and physical therapists should be encouraged to help assess the total needs of the cancer patient and increase the flow of information between disciplines. However, the recommendations of such bodies must not only be recorded: they must also be implemented wherever feasible in order that such conferences continue to serve a valuable function.

--Media campaigns on such subjects as breast self-examination have endeavored to raise the level of public knowledge about cancer. However, such campaigns have focused on the detection and treatment aspects of cancer control. Additional information must be given to the public to help combat the myths and stereotypes that foster social and vocational discrimination against the cancer patient.

--Despite the expansion of government rehabilitation efforts under the National Program for the Conquest of Cancer, the qualitative success of such programs has not yet been assessed. Accordingly, there must be developed an effective mechanism to evaluate at regular intervals the degree to which government rehabilitation programs are



actually meeting the needs of cancer patients.

As Dr. Joseph Cullen has observed, "The history of rehabilitation is yet to come. We have an opportunity to shape it. If we have enough rationalism and resources, we have a chance to shape history that's extremely important." (212)

#### V. Endings and New Beginnings: Continuing Care for Cancer Patients and Their Survivors

Despite the progress that has been made in the control of cancer, the unavoidable truth is that even the most diligent efforts to save a patient are not always successful. According to surgeon Frederic P. Herter of the College of Physicians and Surgeons at Columbia University, there is a "critical point beyond which aggressive therapy is not only dangerous but entirely inappropriate. This point is generally recognizable: profound weakness, loss of appetite and weight, failure of one or more vital organ systems, together mark the beginning of the terminal phase of the illness. Therapy directed at the cancer itself is unavailing at this juncture." (213)

Coping with the fact that his patient will not survive is one of the most taxing aspects of a physician's work. Much of this difficulty may be attributed to a lack of preparation for such a situation. Psychiatrists Bernard Schoenberg and Arthur C. Carr of Columbia University have observed that "inadequate education in the management of the terminally ill probably represents one of the greatest failures in professional education today." (214) A recent study of the attitudes of freshman medical students at Tufts University indicated that

the two most anxiety provoking situations anticipated and actually encountered during their first year of training were discussing a fatal illness with a patient and telling a relative that a patient had died. (215) Apparently such anxieties are widespread. In a nationwide survey of students and deans at 68 medical schools, two-thirds of the students felt that school curricula should be modified to teach the student how to care for the dying patient. (216) Yet the survey of the deans of the same schools revealed that only one-third plan to make any curriculum changes with regard to the care of the dying patient. (217)

The ultimate victim of such omissions in medical school education is not the physician but the patient who has a fatal disease such as terminal cancer. Because of the emphasis of the medical profession on preservation of life, a patient's death may be regarded by a physician as a personal failure, engendering in him feelings of helplessness and ineffectuality. (218) In turn, this may result in anger toward the patient, followed by guilt and emotional withdrawal. (219) Because modern medical care is characterized by a division of labor, the physician can insulate himself from the process of death by delegating specific tasks and responsibilities to others. (220) When such self-protection is assumed, the result is the isolation of the dying patient.

Recent medical literature indicates dying is an experience often characterized by loneliness. Such isolation is both emotional and physical. On the psychological level, it has been found that medical personnel prefer to treat persons who are aware they are dying as

though they were expected to live, and thus effective emotional support for the dying patient is relatively infrequent. (221) On the whole, American nurses and physicians find it difficult to discuss death with patients, unless the patient has already come to terms with his death or is an elderly person whom the staff can assure an "easy" death. (222) Unless a patient shows considerable composure about dying, nurses and physicians tend to lose their composure. (223) A busy hospital staff may have little time to listen to a patient, especially if many patients are competing for attention. (224)

At the same time the hospital staff has emotionally isolated the patient, they have probably physically isolated him, since a dying patient is often moved either to a single room or to a room with a comatose patient. (225) A study by Lawrence LeShan, Ph.D., of the Institute of Applied Biology in New York, compared the length of time it took hospital nurses to respond to call-lights of terminal patients to the time for non-terminal cases. LeShan found that nurses tended to considerably delay answering the ring of the dying, further compounding the isolation of the patient. (226)

As soon as the "death watch" begins, during which nurses keep track of relevant data concerning the gradual recession of clinical life signs, the patient's status as a body becomes more evident. (227) Set in motion is a mechanism of rejection which arises out of procedures designed to operate for the good of the institution. (228) Nurses often urge family members to go home to wait for news there or insist that they wait outside of the patient's room. (229) The

rationale behind such restrictions is often the efficient handling of death within the context of other responsibilities. If a relative is present, it is necessary for a staff member also to be present to demonstrate ongoing concern for the patient. (230)

Thus, as Elizabeth Kubler-Ross (231) and other researchers have found, because of a lack of norms concerning his treatment, as well as his own behavior, the dying person is a special kind of marginal person who must expect "increasing alienation as an almost inevitable aspect of his or her condition." (232, 233)

### The Hospice Concept

One alternative that has been proposed to meet the unique and largely neglected needs of the dying patient is hospice care. The first hospice facility was opened in Dublin in the mid-19th century by Mother Mary Aikenhead, an Irish nun who founded the order of the Irish Sisters of Charity. (234) Since she considered death the beginning of a journey, Mary Aikenhead called her nursing home a hospice after the medieval resting places for pilgrims on their way to the Holy Land. (235) Primarily devoted to caring for terminal cancer patients, other hospices have been established in the 20th century by other religious and secular charitable groups in the United Kingdom. (236)

As a result of the efforts of Dr. Cicely Saunders, the modern hospice movement has expanded the original concept of loving concern for dying patients to include "a solid medical component whose chief characteristic is the sophisticated management of severe pain and other unpleasant symptoms of terminal cancer." (237) Dr. Saunders,



a former nurse and social worker who returned to school at 33 to become a doctor, spent seven years at St. Joseph's hospice in London before establishing the St. Christopher's facility (also in London) with the aid of funds from the National Health Service in 1967. (238)

The sophisticated use of analgesics has been called the hallmark of St. Christopher's. (239) The patient is kept free of the memory and fear of pain by arranging continuous dosages of analgesics so that the patient is always one step ahead of the pain. (240) According to Dr. Saunders, current systems of pain control in hospitals are inadequate, partly due to the 'pharmacological ignorance' of doctors, the fear of the patient's addiction, and of the side effects of drugs on the patient. (241) Dr. Saunders has indicated that patients can be kept from becoming 'insensate zombies' through careful control of medication tailored to the individual's needs. Since so much of the subjective sensation of pain comes from emotional distress, once the patient's fears and anxieties are relieved, dosages can often be lowered. (242)

The hospice facility contains no artificial life support systems. Support for the dying person comes from the atmosphere created by the constant attention of staff (doctors, nurses, social, psychiatric, and religious workers) and volunteers who are always available to listen to the patient, hold his hand, and make him more comfortable. (243) Friends and family--even pets--are allowed to visit at almost any time and spend the day with the patient. (244) Day care facilities are available on the premises for children. (245) According to Dr. Richard Lamerton of St. Joseph's hospice in London, "Above all,

a dying person needs company. There is nothing to do but hold his hand. Hospices have a rule that no one shall die alone. If no relatives can be present, then a nurse or any other sympathetic helper should be with him day or night." (246)

At St. Christopher's, as at other hospices, the unit of care is the family, and the place of care is the patient's home for as long as possible, since most patients prefer to die there. (247) The in-patient facility is seen as a backup unit, and patients often go back and forth between home and the hospice. (248) The health care team makes visits to the patient's home, and social workers and volunteers follow the family after the patient dies to help them adjust to bereavement. (249) (The needs of survivors are discussed further, infra.)

As a result of the efforts of Dr. Lamerton and Dr. Saunders, who have lectured extensively on the hospice concept, some health professionals have become interested in establishing hospice care in the United States. While there were 31 hospice in-patient facilities in the United Kingdom as of 1976 (250), no such facility exists in this country. However, the New Haven, Connecticut, hospice, which has already cared for several hundred cancer patients in its two-and-a-half-year-old home care program, is currently planning to build an in-patient facility in Branford, Connecticut, with the aid of funding from the National Cancer Institute and private foundations. (251) Other home care hospice programs (some of which are also planning to build facilities as soon as funding is available)

are based in Santa Barbara and in Marin County in California and at Georgetown University in Washington, D.C. (252) Various institutions such as Tufts Medical School-Lemuel Shattuck Hospital are incorporating aspects of the hospice philosophy into their systems of care. (253)

In March, 1976, in response to the great surge of interest generated by the New Haven project and in order to further test the feasibility of such care in this country (254), the National Cancer Institute issued a request for proposals from institutions wishing to participate in a field test of the St. Christopher's hospice concept. (255) However, to be eligible for federal funding (which lasts for a maximum of three years), an applicant must already have an existing facility which accommodates 15 to 25 beds and is free standing--i.e., not part of any existing hospital or nursing home. (256) According to Lawrence Burke, program director of the Division of Cancer Control and Rehabilitation, the rationale behind this requirement is that a hospital facility has built into it values and restrictions that are inappropriate as a setting for the implementation of hospice care for the dying patient. (257) Nevertheless, because an offeror must have both a home care program and a separate in-patient facility, the eligibility for such federal funding is obviously limited.

While the philosophy of hospice care has been lauded, the implementation of such care in the United States is fraught with problems. Dr. Melvin Krant feels that hospices may add to the excessive fragmentation, overspecialization, and discontinuity in American medicine. (258)

Dr. Krant and others have observed that grafting an English concept onto American culture may be difficult and that without the English spirit of voluntarism and community feeling, hospices could become more like nursing homes, unless Americans develop their own indigenous variations of such care. (259)

Differences between English and American cultures have also been cited by Cynthia Leitman, former administrator of the hospital emergency service at the University of California at Los Angeles, who, after completing a degree in public health in 1977, will devote her efforts to the implementation of hospice care throughout the United States. "Americans love experts," she stressed. "Most of us believe we need specialized training to deal with death. But the English feel that everyone is a thanatologist because every one of us faces death." (260) She added that because of the American emphasis on technology, many doctors have lost the ability to communicate with their patients and have become estranged from the natural process of death. Thus, patients may be left to help themselves and their families face the impending crisis in their lives. It is to meet such needs that groups such as Make Today Count, a national self-help organization for cancer patients, have been organized. (261) In contrast, the English are less concerned with correct methodology and are more apt to participate as volunteers, drawing on personal coping abilities rather than responses developed as a result of training. (262) Further, the relative homogeneity of the English created by common religious and secular traditions contrasts sharply with the diversity among Americans and thus creates a more fertile



environment for widespread national support of hospice care overseas.

Since there is no comprehensive national health plan in the United States as there is in the United Kingdom, financing hospice care also presents difficulties. Even in cases where federal funding is obtained, questions arise as to the source of funding after such grants terminate. In addition, for the patient and his family, there is currently no insurance plan that covers the cost of hospice care. Under Blue Cross major medical coverage plans, payment is directed to acute care in in-patient facilities and rehabilitative care at home. (263) There is no payment for what is called "custodial care"--i.e., assistance in the activities of daily life, which is the essence of hospice care. (264) Under current Medicare provisions, 100 home care visits subsequent to a hospital stay are covered, but, as with Blue Cross, such visits must be directed to rehabilitation rather than "custodial care." (265) According to Betty Montgomery, R.N., Administrator of the Medical Policy Department at Blue Cross of Southern California, there will be little hope for the implementation of hospice care in this country until there is a major overhaul of our health care system that would provide some type of national health care coverage. (266)

During his April, 1976, lecture tour of the United States, Dr. Lamerton observed that there was an even greater factor inhibiting the acceptance of hospice care in America:

The biggest and most serious impediment was described by the physicians. They dare not, I was told, stop expensive, uncomfortable treatments designed to cure, even in obviously incurable patients, and even though they themselves feel that such inappropriate treatment may be bad medicine.

They dare not because the family of the patient may subsequently sue them for not giving more blood transfusions, drugs, radiation, operations and the like. This is shocking and one is tempted to say that America is getting the health service it deserves. (267)

### Preventive Medicine for the Bereaved

While the future of the hospice concept remains uncertain in the United States, one component of it--the treatment of the dying patient and the family as a unit--deserves further attention at the present time. Under our current system of care, a doctor's avoidance of a dying patient frequently extends to the avoidance of the patient's family. Once the patient dies, he is, in effect, "discharged" so that the contractual basis for the physician's interest and presence is terminated. (268) Yet this is the time that families often require the most support from someone who knew the deceased. (269)

A growing body of research indicates that death may take a heavier toll on survivors than commonly expected. In a 1959 study (270), researchers found a significant increase in mortality among young widowed persons (male and female) as compared with married persons. In the age group 20-34, the annual death rate for widowed persons was found to be more than twice the rate for married persons of either sex among both whites and non-whites. (271)

The highest increase in mortality was attributed to tuberculosis, vascular lesions of the central nervous system, arteriosclerotic heart disease, nonrheumatic chronic endocarditis and other myocardial degeneration, hypertension with heart disease, and general arteriosclerosis. The overall mortality from each of these diseases was at least four times greater among the bereaved than the married. (272) The death rate from tuberculosis and vascular lesions of the central nervous system was particularly high among widowers. (273)

Another study (274) examined the bereavement of widowers aged 55 and over and found that their mortality rate was 1.4 times higher than that of married men; the increase was observed in the first six months of bereavement. Increased mortality rates have also been found among bereaved relatives other than spouses. (275) Over a six-year period researchers followed the lives of a defined population in Wales. The data revealed a significant increase in mortality (restricted to the first year of bereavement) among persons who were bereaved as compared with the mortality rate of a control group. (276) The same study also indicated that the risk of close relatives dying during the first year of bereavement is doubled when the primary death causing the bereavement occurs in a hospital rather than at home. (277)

Other studies have discovered among the bereaved increased incidence of serious psychiatric illness (278), physical illness (279, 280), and, in children who have lost parents, behavior problems such as truancy and pilfering. (281) In addition, the investigations of Lawrence LeShan and others have revealed a correlation

between cancer and certain types of psychological situations. LeShan found that the most consistently reported psychological factor has been the loss of a major emotional relationship prior to the first noted symptoms of the neoplasm. (282)

In view of the research on bereavement, increased efforts are being made to anticipate the needs of survivors and to deal with their problems. One such program is that of the Tufts Psychosocial Cancer Study Unit, formulated in late 1973 with support from the National Cancer Institute. (283) Comprised of psychiatric social workers, research assistants, a full-time clinical psychologist and aided by the services of two psychiatrists and the director, who is a medical oncologist, the team is allied with the oncology units of three nearby hospitals. (284) The Tufts team works with the families of terminal cancer patients before the death of the patient and for six months thereafter. Evaluations of health, mood, and social functioning are made at 6, 12 and 24 months post-death. (285) A recent progress report published by the Unit emphasizes that there is a great need to identify factors in family members that make them vulnerable to poor bereavement outcomes and that much more research is needed in this field. (286)

Thus, while it is true that not every cancer patient can be rehabilitated, the task of rehabilitation does not end with the death of the patient. Instead, the rehabilitation effort must shift from the patient to the survivors in order to prevent their becoming victims of the not uncommon sequela of bereavement which



have been briefly noted. As a result of the efforts of the hospice and other reform movements, the medical profession is developing a greater awareness that there is such a thing as a good death for the terminal cancer patient. It is now time to extend that concern to the patient's family so that there can also be a good life for those left behind.

- (1) American Cancer Society: '75 Cancer Facts and Figures. American Cancer Society, 1974, at 3.
- (2) See note (1).
- (3) See note (1).
- (4) See note (1).
- (5) See note (1) at 4.
- (6) See note (1) at 4.
- (7) Healey, J. E., Jr.: The quality of success in the treatment of cancer. J. Okla. State Med. Assoc. 65:147-151, April, 1972, at 150.
- (8) Healey, J.E., Jr.: Rehabilitation of the patient with cancer. Unpublished chapter (contributed by Dr. Healey) to appear in Nealon, T.F. (ed.): Management of the Patient with Cancer, 2nd ed. Philadelphia, W.B. Saunders, 1976, at 1. (Pagination according to manuscript.)
- (9) Dietz, J.H.: Rehabilitation of the cancer patient: its role in the scheme of comprehensive care. Clin. Bull. 4:104-107, 1974, at 104.
- (10) Interview with Dr. John E. Healey, Jr., Associate Director for Cancer Control at the Comprehensive Cancer Center for the State of Florida, by Myrna Morganstern of HCCP, April 29, 1976, Miami, Fla.
- (11) Ranking disabilities. Am. Rehab. 2:3,5, Sept./Oct., 1976.
- (12) See note (11) at 5.
- (13) See note (9).
- (14) Ewing, J.: Neoplastic Diseases, 4th ed. Philadelphia, W.B. Saunders, 1940, pp. 113-137, at 113.
- (15) See note (14).
- (16) Shimkin, M.B.: Neoplasia. In Bowers, J.Z., and Purcell, E.F. (eds.): Advances in American Medicine: Essays at the Bicentennial (2 vols.). New York, Josiah Macy, Jr., Foundation, 1976, vol. 1, pp. 210-250. Quoted in the UCLA Cancer Center Bulletin 3:5:9, 1976.

- (17) See note (16).
- (18) Feldman, F.L.: Work and Cancer Health Histories: A Study of the Experiences of Recovered Patients. San Francisco, California Division of the American Cancer Society, 1976.
- (19) See note (18) at 9.
- (20) See note (18) at 10.
- (21) See note (18) at 71-74 and 92.
- (22) See note (18) at 76-80 and 92.
- (23) See note (18) at 68-70 and 93.
- (24) See note (18) at 74 and 93.
- (25) See note (18) at 75 and 93.
- (26) See note (18) at 83 and 93-94.
- (27) See note (18) at 83-84 and 94.
- (28) See note (18) at 83.
- (29) See note (18) at 1.
- (30) See note (18) at 71-72.
- (31) See note (18) at 162.
- (32) See note (18) at 117-119 and 162.
- (33) See note (18) at 162.
- (34) See note (18) at 94.
- (35) A.B. 1194, the "Siegler Bill," became effective January 1, 1976, amending seven sections of the California Fair Employment Practices Act of the Labor Code. Stats. 1975, c. 431, sections 1-7.
- (36) See note (18) at 187.
- (37) Roth, J.A., Eddy, E.M.: Rehabilitation for the Unwanted. New York, Atherton, 1967, at 3.

- (38) Pattison, H.A.: The Handicapped and Their Rehabilitation. Springfield, Ill., Charles C. Thomas, 1957, at 1 and 10-11.
- (39) See note (7) at 148.
- (40) Krant, M. J.: Problems of the physician in presenting the the patient with the diagnosis. In Cullen, J.W., Fox, B.H., and Isom, R.N. (eds.): Cancer: The Behavioral Dimensions. National Cancer Institute Monograph. New York, Raven Press, 1976, pp. 269-274, at 270-271.
- (41) See note (9) at 105.
- (42) See note (9) at 105.
- (43) Cobb, A.B.: Medical and psychological problems in the rehabilitation of the cancer patient. In Hardy, R.E., and Cull, J.G. (eds.): Counseling and Rehabilitating the Cancer Patient. Springfield, Ill., Charles C. Thomas, 1975, pp. 24-68, at 51.
- (44) Proceedings of the 1967 conference on rehabilitation problems of the patient with cancer of the head and neck. In Healey, J.E., Jr. (ed.): Ecology of the Cancer Patient. Washington, D.C., Interdisciplinary Communication Associates, Inc., 1970, Part I, pp. 19-70, at 19.
- (45) See note (44) at 20.
- (46) See note (44) at 20.
- (47) See note (44) at 26.
- (48) See note (44) at 26.
- (49) See note (44) at 27.
- (50) Henke, R., Coleman, D.: Some social, psychological, and vocational implications of laryngectomy. Am. Rehab. 1:19-22, July/Aug., 1976, at 19.
- (51) See note (50).
- (52) See note (50).
- (53) See note (44) at 27.
- (54) See note (44) at 27.



- (55) See note (50) at 21.
- (56) Gardner, W.H.: Laryngectomy Speech and Rehabilitation. Springfield, Ill., Charles C. Thomas, 1971, at xi.
- (57) See note (56).
- (58) See note (56).
- (59) Gutzmann, H.: Stimme und sprache ohne kehlkopf. Z. Laryng. Rhinol. Otol. 1:221, 1909.
- (60) Diedrich, W.M., Youngstrom, K.A.: Alaryngeal Speech. Springfield, Ill., Charles C. Thomas, 1966, at 220.
- (61) See note (56).
- (62) See note (56).
- (63) See note (50) at 21.
- (64) See note (44) at 29.
- (65) See note (44) at 29-30.
- (66) See note (44) at 29.
- (67) See note (50) at 20.
- (68) Snidecor, J.C.: Speech Rehabilitation of the Laryngectomized. Springfield, Ill., Charles C. Thomas, 1969, at 200.
- (69) See note (68).
- (70) See note (68) at 200ff.
- (71) See note (56) at 55.
- (72) See note (56) at 57.
- (73) See note (50) at 21.
- (74) Zwitman, D.H.: Speech rehabilitation for the laryngectomy patient. UCLA Cancer Center Bull. 3:4-5, Feb./March, 1976, at 4.
- (75) See note (74).

- (76) Telephone interview with Dr. Daniel H. Zwitman, Assistant Professor of Surgery in the Head and Neck Division at UCLA and Director of the UCLA Speech Clinic, by Myrna Morganstern of HCCP, November 5, 1976, Los Angeles, Ca.
- (77) See note (76).
- (78) See note (43) at 53.
- (79) See note (43) at 53.
- (80) See note (44) at 35.
- (81) See note (44) at 57.
- (82) Rosillo, R.H., Graham, W.P.: The long term adjustment of the patient with head and neck cancer: I. Work, social, and heterosexual activity levels. J. Surg. Onc. 4:439-446, December, 1972, at 443.
- (83) See note (82).
- (84) See note (82) at 445.
- (85) See note (1) at 15.
- (86) See note (1) at 7.
- (87) Dietz, J.H.: Rehabilitation of the cancer patient. Med. Clin. N. Amer. 53:607-624, May, 1969, at 615.
- (88) See note (87).
- (89) See note (87).
- (90) Healey, J.E., Jr., Villaneuva, R.: Cancer of the breast: the role of rehabilitation medicine. In Rehabilitation of the Cancer Patient, proceedings of the Annual Clinical Conference on Cancer at the University of Texas M.D. Anderson Hospital and Tumor Institute at Houston, Texas, 1970. Chicago, Yearbook Medical Publishers, 1972, pp. 191-201, at 199.
- (91) See note (8) at 14.
- (92) See note (8) at 14.
- (93) See note (8) at 14.
- (94) See note (8) at 14-15.

- (95) See note (8) at 15.
- (96) See note (90).
- (97) See note (90).
- (98) See note (90) at 197.
- (99) See note (90) at 197-198.
- (100) See note (90) at 198.
- (101) See note (90) at 198.
- (102) See note (90) at 198.
- (103) Telephone interviews with Mrs. Terese Lasser, National Consultant and Coordinator of the Reach to Recovery Program of the American Cancer Society, by Myrna Morganstern of HCCP, November 5 and November 9, 1976, New York City.
- (104) See note (103).
- (105) See note (103).
- (106) See note (103).
- (107) Harrell, H.C.: Rehabilitation--quality of survival. In Rehabilitation of the Cancer Patient (see note 90), pp. 175-177, at 176.
- (108) Markel, W.B.: Rehabilitation after mastectomy. In Proceedings of the Seventh National Cancer Conference, sponsored by the American Cancer Society and the National Cancer Institute, September 27-29, 1972. J.B. Lippincott, Philadelphia, 1973, pp. 851-852, at 851.
- (109) See note (108).
- (110) Kushner, R.: Breast Cancer: a personal history and an investigative report. New York, Harcourt Brace Jovanovich, 1975, at 169 ff.
- (111) Interview with Dr. Joseph Cullen, Deputy Director of the UCLA Cancer Center, by Myrna Morganstern of HCCP, September 30, 1976, Los Angeles, Ca.
- (112) See note (110).
- (113) See note (111).

- (114) Benfield, J.R.: Current attitudes about breast masses in women. UCLA Cancer Center Bull. 3:2 and 4, June/July, 1976.
- (115) See note (114) at 2.
- (116) See note (114) at 4.
- (117) Trachtenberg, J.M.: Team involvement and the problems incurred. In Rehabilitation of the Cancer Patient (see note 90), pp. 181-189, at 183.
- (118) See note (90) at 193.
- (119) See note (90) at 193.
- (120) See note (111).
- (121) See note (40) at 273.
- (122) Healey, J.E., Jr.: Role of rehabilitation medicine in the care of the patient with breast cancer. Cancer 28:1666-1671, 1971, 1667.
- (123) See note (117) at 182.
- (124) See note (117) at 187.
- (125) Eisenberg, H.S., Goldenberg, I.S.: Measurement of quality of survival of breast cancer patients. In Hayward, J.L., and Bulbrock, R.D. (eds.): Clinical Evaluation in Breast Cancer. London, Academic Press, 1966, pp. 93-108.
- (126) Schottenfeld, D., Robbins, G.F.: Quality of survival among patients who have had radical mastectomy. Cancer 26:650-655, 1970.
- (127) Telephone interview with Dr. David Schottenfeld, Chief of Clinical Epidemiology and Statistics at Memorial Hospital for Cancer and Allied Diseases in New York City, by Myrna Morganstern of HCCP, November 5, 1976, New York City.
- (128) See note (126) at 651.
- (129) See note (127).
- (130) See note (126) at 651.
- (131) Rowbotham, J.L.: Proper care of abdominal stomas. Geriatrics 29: 56-63, October, 1974, at 57.



- (132) See note (131).
- (133) See note (131).
- (134) See note (131).
- (135) See note (1) at 17.
- (136) Dietz, J.H.: Rehabilitation needs of patients with colostomy, ileostomy, or artificial bladder. In Rehabilitation of the Cancer Patient (see note 90), pp. 237-240, at 239.
- (137) See note (136).
- (138) Proceedings of the 1969 conference on rehabilitation of the patient with cancer of the pelvic visceral organs. In Healey, J.E., Jr. (ed.): Ecology of the Cancer Patient. Washington, D.C., Interdisciplinary Communication Associates, Inc., 1970, Part III, pp. 117-161, at 125.
- (139) See note (138).
- (140) See note (138) at 126.
- (141) McCawley, A., Mannix, H., Jr., McCarthy, D.D.: The psychological problems of ostomates. Conn. Med. 39:151-155, March, 1975, at 151.
- (142) See note (141).
- (143) Lenneberg, E.: Continuing needs of patients with an abdominal stoma. In Rehabilitation of the Cancer Patient (see note 90), pp. 225-236, at 227 and 228.
- (144) Benfield, J.R., Fowler, E., Barrett, P.: Enterostomal therapy. Arch. Surg. 107: 62-65, July, 1973, at 63.
- (145) Telephone interview with Virginia Sinon, Assistant to the Vice-President for Service and Rehabilitation of the American Cancer Society, by Myrna Morganstern of HCCP, January 13, 1977, New York City.
- (146) Lenneberg, E.: The role of enterostomal therapists and stoma rehabilitation clinics: a second look. Cancer 34: 977-982, at 979.
- (147) See note (146).
- (148) Turnbull, R.B., Jr.: Rehabilitation of the stomal patient. In Proceedings of the Seventh National Cancer Conference (see note 108), pp. 847-848, at 847.

- (149) See note (148).
- (150) See note (144) at 64.
- (151) Telephone interview with Evonne Fowler, R.N.E.T. at Harbor General Hospital, by Myrna Morganstern of HCCP, November 9, 1976, Los Angeles, Ca.
- (152) See note (151).
- (153) See note (151).
- (154) See note (151).
- (155) See note (151).
- (156) U.S. Congress, Senate: Rehabilitation Act of 1972: A Report. 93rd Congress, 1st Session. Senate Committee on Labor and Public Welfare, Report #93-48, at 5.
- (157) Gellman, W.: Fundamentals of rehabilitation. In Garrett, J.F., and Levine, E.S. (eds.): In Rehabilitation Practices with the Physically Disabled. New York, Columbia University Press, 1973, pp. 3-39, at 7.
- (158) See note (156) at 6.
- (159) See note (156) at 6.
- (160) See note (157) at 8.
- (161) See note (138) at 159.
- (162) See note (8).
- (163) See note (8) at 4.
- (164) See note (8) at 5.
- (165) Samuelson, K.M., Cecil, O.: Rehabilitation and cancer. In Counseling and Rehabilitating the Cancer Patient (see note 43), pp. 3-23, at 21.
- (166) State Vocational Rehabilitation Agency Fact Sheet Booklet for Fiscal Year 1975. USDHEW, Office of Human Development, Rehabilitation Services Administration, Washington, D.C., 1976, at 1.
- (167) See note (166).

- (168) Final Report on Characteristics of Clients Rehabilitated During Fiscal Year 1974. USDHEW, Office of Human Development, Rehabilitation Services Administration, Washington, D.C., Information Memorandum RSA-IM-76-87, June 22, 1976, p. 12, at note 7. Supplementary 1975 data supplied by Mr. Lawrence Mars, statistician, Rehabilitation Services Administration, September, 8, 1976.
- (169) U.S. Congress, Senate. Committee on Labor and Public Welfare. Hearings to Amend the Rehabilitation Act of 1973 before the Senate Committee on Labor and Public Welfare, January 10 and February 6, 1973. Washington, D.C., U.S. Govt. Printing Office, 1973, at 4-5.
- (170) See note (169) at 425.
- (171) See Book Two, Chapter 7 of this work.
- (172) See note (171).
- (173) See note (171).
- (174) See Book Two, Chapter 6 of this work.
- (175) Rehabilitation Planning Report: National Cancer Rehabilitation Planning Conference Chairman's Report. USDHEW, National Cancer Institute, June 19, 1973.
- (176) See note (175) at p. 2-1.
- (177) See note (175) at p. 2-5.
- (178) Commission on Chronic Illness: Chronic Illness in the United States (2 vols.). Cambridge, Harvard University Press, 1956.
- (179) See note (178), vol. 2, at 427.
- (180) See note (178), vol. 2, at 434.
- (181) See note (178), vol. 2, at 437.
- (182) See note (178), vol. 2, at 439.
- (183) Cooper, E.F.: Community services in support of the cancer patient. In Schottenfeld, D. (ed.): Cancer Epidemiology and Prevention. Springfield, Ill., Charles C. Thomas, 1975, pp. 457-465, at 458.
- (184) See note (183) at 459.

- (185) Interview with Dr. William B. Markel, Vice-President for Service and Rehabilitation of the American Cancer Society, by Devra Breslow of HCCP, May 21, 1976, New York City.
- (186) Telephone interview with Helene Brown, Executive Director of Community Cancer Control in Los Angeles for the American Cancer Society, by Myrna Morganstern of HCCP, November 3, 1976, Los Angeles, Ca.
- (187) See note (185).
- (188) See note (185).
- (189) Lasser, T.: Reach to Recovery. New York, American Cancer Society, 1974, at 6-9.
- (190) Reach to Recovery. Pamphlet published by the American Cancer Society, revised October, 1975.
- (191) See note (103).
- (192) See note (103).
- (193) See note (185).
- (194) See note (185).
- (195) See note (185).
- (196) See note (185).
- (197) See note (185).
- (198) See note (185).
- (199) See note (185).
- (200) See note (103).
- (201) Holleb, A.: The American Cancer Society--a voluntary health agency's contribution to rehabilitation. In Rehabilitation of the Cancer Patient (see note 90), pp. 293-296, at 293-294.
- (202) Rehabilitating Laryngectomees. Pamphlet published by the American Cancer Society, 1973.
- (203) See note (202), at 7-8.
- (204) See note (202) at 4 and 7.
- (205) See note (185).



- (206) See note (202) at 8.
- (207) See note (185).
- (208) See note (185).
- (209) Lenneberg, E., Mendelssohn, A.N.: Colostomies--A Guide. Los Angeles, United Ostomy Association, 1971, at 33.
- (210) General Information Sheet (mimeo). Published by the United Ostomy Association of Los Angeles, April, 1976, at 1.
- (211) See note (210).
- (212) See note (111).
- (213) Herter, F.P.: A surgeon looks at terminal illness. In Schoenberg, B., Carr, A.C., Peretz, D., and Kutscher, A.H. (eds.): Psychosocial Aspects of Terminal Care. New York, Columbia University Press, 1972, pp. 79-87, at 85.
- (214) Schoenberg, B., Carr, A.C.: Educating the health professional in the psychosocial care of the terminally ill. In Psychosocial Aspects of Terminal Care (see note 213), pp. 3-15, at 3.
- (215) Saul, E.V., Kass, J.S.: Study of anticipated anxiety in a medical school setting. J. Med. Educ. 44:526, 1969.
- (216) See note (214) at 6.
- (217) See note (214) at 4.
- (218) See note (214) at 9-10.
- (219) See note (214) at 9-10.
- (220) See note (214) at 10.
- (221) Duff, R.S., Hollingshead, A.B.: Sickness and Society. New York, Harper and Row, 1968, at 306-330.
- (222) Quint, J.C.: The Nurse and the Dying Patient. New York, Macmillan, 1967, at 77-112. See also Quint, J.C.: The dying patient: a difficult nursing problem. Nurs. Clin. North Am. 2:763-773, December, 1967.
- (223) Strauss, A.L., Glaser, B.G.: Patterns of dying. In Brim, O.G., Jr., Freeman, H., Levine, S., and Scotch, N.A. (eds.): The Dying Patient. New York, Russell Sage Foundation, 1970, pp. 129-155.

- (224) See note (223) at 146-147.
- (225) See note (223) at 147-148.
- (226) Crane, D.: Dying and its dilemmas as a field of research. In The Dying Patient (see note 223), pp. 303-325, at 314.
- (227) Sudnow, D.: Dying in a public hospital. In The Dying Patient (see note 223), pp. 191-208, at 194.
- (228) See note (227).
- (229) See note (227) at 195.
- (230) See note (227) at 195.
- (231) Kubler-Ross, E.: On Death and Dying. New York, Macmillan, 1969.
- (232) See note (226) at 315.
- (233) See note (231) at 7-9 and 218-239.
- (234) Lamerton, R.: Care of the Dying. London, Priory Press Ltd., 1973, at 15.
- (235) See note (234).
- (236) See note (234) at 43-44.
- (237) Holden, C.: Hospices: For the dying, relief from pain and fear. Science 193:389-319, July 30, 1976, at 389.
- (238) See note (237) at 390.
- (239) See note (237) at 390.
- (240) See note (237) at 390.
- (241) See note (237) at 390.
- (242) See note (237) at 390.
- (243) See note (237) at 390.
- (244) See note (237) at 390.
- (245) Kron, J.: Designing a better place to die. New York, March 1, 1976, pp. 43-49, at 46.

- (246) See note (234) at 54.
- (247) See note (245) at 43.
- (248) See note (245) at 43.
- (249) See note (245) at 43.
- (250) Implementation of the "Hospice" Concept for the Care of Terminal Cancer Patients (mimeo). DHEW, National Institute of Health RFP No. NO1-CN-65375-05, March 29, 1976, at 24.
- (251) See note (245) at 47.
- (252) Craven, J., Wald, F.S.: Hospice care for dying patients. Am. J. Nursing 75:1816-1822, October, 1975, at 1816.
- (253) Krant, M.J.: In the context of dying. In Psychosocial Aspects of Terminal Care (see note 213), pp. 201-209.
- (254) Telephone interview with Mr. Lawrence Burke, Program Director at the Division of Cancer Control and Rehabilitation of the National Cancer Institute, by Myrna Morganstern of HCCP, January 7, 1977, Bethesda, Md.
- (255) See note (250).
- (256) See note (250) at 30.
- (257) See note (237) at 391.
- (258) See note (237) at 391.
- (259) See note (237) at 391.
- (260) Interview with Cynthia Leitman, graduate student at the UCLA School of Public Health, by Myrna Morganstern of HCCP, September 17, 1976, Los Angeles, Ca.
- (261) Pellman, D.R.: "Learning to live with dying." New York Times Magazine, December 5, 1975, 44-94 et passim.
- (262) See note (260).
- (263) Telephone interview with Betty Montgomery, R.N., Administrator of the Medical Policy Department of Blue Cross of Southern California, by Myrna Morganstern of HCCP, November 22, 1976, Los Angeles, Ca.
- (264) See note (263).

- (265) Telephone interview with Edward Altuna, Medicare Contact Representative, Santa Monica branch office, by Myrna Morganstern of HCCP, November 22, 1976, Santa Monica, Ca.
- (266) See note (263).
- (267) Lamerton, R.: Letter to the Los Angeles Times. Opinion/Editorial Page, April 26, 1976.
- (268) Sudnow, D.: Passing On. Englewood Cliffs, N.J., Prentice-Hall, 1967, at 81.
- (269) See note (268).
- (270) Kraus, A.S., Lilienfeld, A. M.: Some epidemiologic aspects of the high mortality in the young widowed group. J. Chron. Dis. 10:207-217, 1959.
- (271) See note (270).
- (272) See note (270).
- (273) See note (270).
- (274) Parkes, C.M., Benjamin, B., Fitzgerald, R.G.: Broken heart: a statistical study of increased mortality among widowers. Brit. Med. J. 1:740-743, 1969.
- (275) Rees, W.D., Lutkins, S.G.: Mortality of bereavement. Brit. Med. J. 4:13-16, 1967.
- (276) See note (275).
- (277) See note (275).
- (278) Parkes, C.M. Bereavement and mental illness, Parts I and II. Brit. J. Med. Psych. 38:1-26, 1965.
- (279) Maddison, D., Maddison, V.: The health of widows in the year following bereavement. J. Psychosom. Res. 12:297-306, 1968.
- (280) Parkes, C.M., Brown, R.J.: Health after bereavement: a controlled study of young Boston widows and widowers. Psychosom. Med. 34:449-461, 1972.
- (281) Bonnard, P.: Truancy and pilfering associated with bereavement. In Lorand, S., and Schneer, L.S. (eds.): Adolescents: Psycho-analytic Approach to Problems and Therapy. New York, Harper and Row, 1961, pp. 152-179.



- (282) LeShan, L.: Psychological states as factors in the development of malignant disease: a critical review. J. Nat. Cancer Inst. 22:1-18, January, 1959.
- (283) Krant, M.J., Beiser, M., Adler, G., et al: The role of a hospital-based psychosocial unit in terminal cancer illness and bereavement. J. Chron. Dis. 29:115-127, 1976.
- (284) See note (283).
- (285) See note (283).
- (286) See note (283).



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